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Post marketing stability studies of artesunate tablets

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Dedication

I dedicate this work:

To the souls of my parents.

To my brothers and sisters who have supported me through my study.

To my colleagues in the National Drug Quality Control Laboratory.

They have all made it what it is.

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Contents

List of Figures

List of tables

List of appendix

Abstract

Objective

1. To conduct a post-marketing surveillance of different artesunate formulations used in Sudan.
2. To assess the effect of transport and storage conditions, at different regions of Sudan, on the stability of artesunate tablets.
3. To adopt an HPLC dissolution test method suitable for evaluating the artesunate drug release.

Methodology

1. Stability of artesunate tablets was evaluated. Three procedures were used for the evaluation:

   1.1. Four states in Northern, Eastern, Western, and Central of Sudan were chosen for sample collection in post-marketing study to represent all Sudanese market. The sampling procedure was designed in a way to determine whether the products were adversely affected by the transport and storage conditions at these states.

   1.2. Artesunate tablets were stored in different parts of the country (Khartoum, Elobied, Port Sudan and Atbara) which represent different climatic conditions in Sudan. Samples were taken for analysis at various time intervals.

1.3. Five generic brands of artesunate tablets were stored at room temperature and subjected to various compendia tests.

2. An HPLC dissolution method was adopted and applied for analysis of artesunate tablets. The method was compared with the official UV-spectrophotometric method (Chinese pharmacopeia method 1996).

Results

The results of post-marketing surveillance identified several significant problems in the stability of artesunate tablets in all states. There was a percentage failure of 12% in the first year and 4% in the second year for different generic brands of artesunate tablets in Sudanese market. There was a percentage failure of 100% in one generic brand of artesunate with regard to content and dissolution test. There was a failure of 76% in one generic brand due to dissolution test. Almost 98% failures were due to dissolution rate, followed by 7% failure due to dissolution and assay (content of the active substance), and 2% failure due to physical appearance. The results showed a higher failure level in the public sector (14%) than the private supply system (2%)

The results of the stability studies at room temperature indicated the presence of degredant resulting from the effect of high temperature and humidity. The degradant was one of the dihydoartemisinin namely α-dihydoartemisinin (α-DHA). However, the degradant, content of active substance and all other results of analysis of the product were within the

pharmacopeias specification limits (IP, 2005; Chinese pharmacopeia, 1996).

Analysis of different generic brands showed failure in dissolution test of all batches of one generic brand after three months storage at room temperature. One generic brand reached the lower limit (60%) of the dissolution test at the end of its shelf life (24months).

The adopted HPLC dissolution test method of the artesunate tablets was validated .The results showed good linearity in the range of 40-120 µg/ml of artesunate tablets with correlation coefficient of 0.999.The results of the developed HPLC method were compared with the official UV-spectrophotometric method (Chinese pharmacopeia method 1996). The results of the adopted method showed no significant difference from the official method. The calculated F-values between the adopted method and official method were found less than the tabulated ones which which confirm that the method is precise. The accuracy of the prescribed method was evaluated using t-tests. All the calculated t-values were found less than tabulated ones. Thus the adopted method is accurate. The adopted method was repeatable and reproducible as shown by calculating the relative standard deviations (RSD) in two different laboratories. All the data were found within the acceptance criteria of 5% which confirm that the adopted method is precise.

Conclusion:

The results of the present work revealed the presence of substandard antimalarial products circulating in Sudanese market. This appears to be

due to non-appropriate storage conditions and/or non-compliance with GMP guidelines by manufacturers in productions. The detection of poorly formulated artesunate tablets among different brands highlights the need for increasing drug surveillance and monitoring of the quality of antimalarial medicines currently in use so as to overcome treatment failure.

The stability of artesunate tablets is affected by high temperature and humidity. Thus the product(s) should be appropriately blister-packed and stored in a cool dry place to assure maximal stability and product integrity.

The adopted dissolution method for artesunate tablets is selective and reproducible and can be employed in poorly equipped laboratories like those found in most developing countries.

مستخلص الأطروحه

الأهداف

1. إجراء مرحلة ما بعد التسويق لمختلف مركبات الأرتيسونات المتداولة بالسودان.
2. تقييم تأثير ظروف النقل والتخزين في أنحاء مختلفة من السودان فى ثبات أقراص الأرتيسونات.
3. إعتماد طريقة إختبار الذوبانية لأقراص الأرتيسونات بإستخدام جهاز الكروماتوغرفيا السائل عالى الجوده.

منهجية البحث

1. تقييم ثبات أقراص الأرتيسونات. وقد استخدمت ثلاثة إجراءات للتقييم:

1.1 إختيار أربعة أقاليم في شمال وشرق وغرب ووسط السودا ن، تمثل السوق السودانى، لجمع العينات في مرحلة ما بعد التسويق . إجراءات أخذ العينات تم تصميمها بحيث يثبت تحديد ما إذا كانت هذه المنتجات تتأثر سلبا في حالة النقل والتخزين.

1.2 تخزين أقراص الأرتيسونات في مناطق مختلفة من البلاد (الخرطوم ، الأبيض ، بور تسودان وعطبرة) لتمثل مختلف الظروف المناخية في السودان ، وتم أخذ عينات لتحليلها في فترات مختلفة.

1.3 تخزين خمس ماركات تجارية عامة من أقراص الأرتيسونات في درجة حرارة الغرفة ، وأخضعت لاختبارات دستوريه مختلفة.

2. تطبيق أسلوب اختبار الذوبانيه المعتمدة لتحليل حبوب الأرتيسونات بإستخدام جهاز الكروماتوغرفيا السائل عالى الجوده، ومقارنة النتائج مع الطريقه الدستوريه التى يستخدم فيها جهاز الأشعة فوق البنفسجية(طريقة التحليل بدستور الادوية الصينى لعام 1996).

النتائج

نتائج المتابعة بعد التسويق أوضحت عدة مشاكل فى ثبات أقراص الأرتيسونات في كل الأقاليم. هنالك نسبة فشل 12% فى السنة الأولى و4% فى السنه الثانيه لمختلف منتجات الأرتيسونات في السوق السودانية. كانت هنالك نسبة فشل 100% لأحد مستحضرات الأرتيسونات في محتوى الماده الفاعله ، واختبار الذوبانيه والمظهر الخارجى للأقراص بينما فشل مستحضر اخر بنسبة 76% نتيجة لاختبار الذوبانيه. تقريبا 98% من الفشل كان فى اختبار الذوبانيه ، تليها 7% نسبة فشل فى الذوبانيه ومحتوى المادة الفعالة و2% نسبة فشل فى المظهر الخارجى . أظهرت النتائج ارتفاع مستوى الفشل في القطاع العام 14 % عنها فى القطاع الخاص 2%.

النتيجة التي تم الحصول عليها من دراسات الثبات لأقراص الأرتيسونات في درجة حرارة الغرفة أوضحت ظهور تحلل لأقراص الأرتيسونات الموجودة في جميع أنحاء البلاد نتيجة لتأثير درجة الحرارة والرطوبة حيث وجد أحد مركبات الديهيدروارتميسنين كأحد النواتج. على الرغم من ذلك فإن نتائج تحليل المواد المشا ة و التحاليل الأخرى للمنتج وجدت ضمن المواصفات الدستورية]دستور الأدوية العالمى لعام 2005 و دستور الأدوية الصينى لعام 1996) .

تحليل الماركات التجارية العامة للعقار أظهرت نسبة فشل لإختبار الذوبانية لأحدها بعد مرور ثلاثه أشهر على تخزينه.بينما وصل أدنى مستوى عتد اية العمر الحقيقى فى ماركة أخرى.

تم التحقق من طريقة إختبار الذوبانية المعتمدة لأقراص الأرتيسونات بإستخدام جهاز الكروماتوغرفيا السائل عالى الجوده حيث أعطت النتائج علاقه خطية قوية فى المدى 40-120 ميكروجرام/مل بمعامل إرتباط0.999 . تمت مقارنة نتائج إختبار الذوبانية المعتمدة مع الطريقة الدستورية التى يستخدم فيها جهاز الأشعة فوق البنفسجية (الدستور الصينى لعام 1996) وأظهرت النتائج عدم اختلاف بين الطريقة المعتمدة والطريقة الدستورية وبحساب قيمة F بين نتائج الطريقتين وجدت أقل من تلك القيم ا دولة مما يؤكد دقة

الطريقة المعتمدة . وقد تم إجراء التحاليل عدة مرات فى معملين مختلفين لمعرفة مدى تواتر نتائج التحليل بتلك الطرق وذلك بحساب قيمة t التى وجدت أقل من ا دولة مما يوكد تواتر نتائج التحليل . أثبتت الدراسة أيضاً أن الطريقة المعتمدة هى ذات مصداقية وتعطى نفس النتائج بتكرارها وذلك بتحديد درجة الإنحراف المعيارى النسبى والتى لم تتعدى 5% لكل التشغيلات المستخدمة.

الخلاصة :

تشير البيانات إلى مشكلة كبيرة تتمثل فى وجود مضادات للملاريا متدنية الجوده متداولة وقد يعزى ذلك إلى ظروف التخزين غير المناسبة وعدم الامتثال للتوجيهات السليمه فى أسلوب التصنيع الجيد من قبل الشركات المصنعة.

الكشف عن وجود بعض التراكيب متدنية الصنع لأقراص الأرتيسونات بين مختلف الماركات يسلط الضوء على الحاجة لزيادة مراقبة ورصد جودة الأدوية المضادة للملاريا التي تستخدم حاليا وذلك للحيلولة دون فشل فاعلية العلاج.

ينبغي أن تكون منتجات عقار الأرتيسونات معبأة بشكل مناسب وتخزن في مكان بارد لضمان أقصى قدر من الثبات وسلامة المنتجات.

طريقة إختبار الذوبانية المعتمدة لأقراص الأرتيسونات دقيقة,قابلة للتطبيق ويمكن استخدامها في مختبرات مجهزة تجهيزاً بسيطاً مثل تلك الموجودة في معظم البلدان النامية.

List of abbreviations

Abs.	Absorbance
AUP	Area under the peak
APIs	Active pharmaceutical ingredients
AS+SP	Co-blister Artesunate+lSulphadoxine Pyremethamine tablets
ART+LUM	Co-blister Artemether+lumefantrine tablets
ACTs	Artemisinin based combination therapy
AC	Air conditioner
AD	Anno Domini
APCI	Atmospheric pressure chemical ionization
BP	British Pharmacopeia
Batch No	Batch number
CMC	Central Medical Supply
DHA	Dihydroartemisinin
DGP	Directorate General of Pharmacy
D.T	Disintegration test
FDA	Food and Drug Administration
EMEA	The European Agency for Evaluation of Medicinal Products.
GMC	General Medical Company
GC	Gas chromatography
GMP	Good Manufacturing Practice
HPLC	High performance liquid chromatography

H.F	Health facilities
hr	Hour
IP	International Pharmacopoeia
ICH	International Conference on Harmonization
min	Minute
MS	Mass spectrometry
N	Number of samples analyzed
NDQCL	National Drug Quality Control Laboratory -Khartoum
NCL	National Chemical Laboratory-Khartoum
NMP	National Malaria Control Program -Sudan
PPRO	The Pharmacy and Poisons Act, and Regulations and 0rder
rel	Release
RSD	Relative standard deviation
R.S	Related substance
rpm	Rotation per minute
RH	Relative humidity
SD	Standard Deviation
TLC	Thin layer chromatography
U.V	Ultra violet
USP	United State Pharmacopeia
WHO	World Health Organization

Chapter 1
Introduction

1.1. Post -marketing surveillance

Post-marketing surveillance is the practice of monitoring a pharmaceutical drug or device after it has been released to the market (EMEA, 2000). It confirms the safety of a drug after it is used in the general population by a large number of people who have a wide variety of medical conditions. Post-marketing surveillance plays an important role to discover undesirable effects that might be present. It provides additional information on the benefits and risks of a drug, resulting in possible drug safety hazards being identified which may influence the benefit/risk ratio of medicinal product (FDA, 2007). Public health research has neglected investigations of the quality of essential medicines, with few reliable data despite evidence suggesting that it is a major problem reducing the effectiveness of health care (Taylor et al, 2001; Caudron, et al, 2008). There are very few reliable published estimates of the prevalence of counterfeit, substandard or degraded medicines for any country (Newtonet al, 2006). Differentiation between counterfeit, substandard or degraded products is important as this information is vital to allow medicine regulatory authorities to determine appropriate counter-measures. Since the 1990s, substandard drugs used for the treatment of potential-fatal tropical diseases, such as malaria, have been detected in increasing numbers. Malaria is a major health problem in many tropic countries, especially in Sub-Saharian Africa and Southeast Asia. Each year, there are approximately 515 million cases of malaria, killing between one and three million people, the majority of whom are young children in Sub-Saharian Africa (Amin et al,2005). Malaria is a major cause of morbidity and mortality in Sudan resulting in an estimated 7.5 million cases and 35,000 deaths annually (Malik et al, 2004).In the late 1990s, great efforts were directed to improve malaria cases management and this was included in the development of the Roll Back Malaria (RBM)

strategic plan in 2001(Malik and Saeed , 2004). Case management requires the provision of prompt, effective and safe treatment to malaria cases (Jane, 2005).Combin-ation therapies preferably using "novel" antimalarial drugs with different modes of action is the way forwarded for improving therapeutic efficacy and delaying development of resistance in antimalarial chemotherapy. Artemi-sinin based combinations have several distinct advantages in that they produce rapid clinical and parasitological cure. To our knowledge there is as yet no documented parasite resistance. They reduce gametocyte carriage rate, and are generally well tolerated (Jane, 2005). artemisinin- derivatives are now the recommended treatment in many countries where drug resistant malaria parasites exist and have become the target of an extremely sophisticated and prolific counterfeit drug trade. Since the 1970s, chloroquine resistance has been documented and has since increased and spread all over Sudan (Stivanello et al, 2004). Using the results of research on resistance to chloroquine, Sudanese policy-makers updated their national malaria treatment guidelines in 2004 to artemisinin-based combination therapy (ACTs), both as first-line (AS+SP) and second-line (ART+LUM) (Malik et al, 2006). Policy makers at General Directorate of Pharmacy were highly concerned about the availability of artemisinin derivative–based combination therapy(ACTs) and their stability in hot weather, such as Sudan, as no company at time of launching the new policy was qualified by WHO to provide co-blister of AS+SP,(Malik et al, 2006). These combination options need continued documentation of safety and efficacy as part of any potential implementation process, especially among very young children, pregnant women, and breast feeding mothers and their babies (Sivong et al, 2009). In many settings, antimalarial therapy is usually complicated not only because of drug resistance but also patient-related factors, such as poor adherence to therapy, drug side-effects, such as vomiting, which lead to under-dosage, drug interactions and

individual variations (WHO, 2005). Therapeutic failure also occur due to pharmaceutical failure resulting from poor quality of products, instability of products, which leads to deterioration of their quality before they reach the patient, or the use of counterfeit products. Several WHO-sponsored studies have demonstrated significant instability of products during transport by sea, and also during road transfer to final destination (WHO,2005), the quality of antimalarials (chloroquineand sulphadoxine / pyrimethamine) in selected African countries (Gabon, Ghana, Kenya, Mali, Mozambique, Sudan, the United Republic of Tanzania and Zimbabwe) had been studied .The data indicated significant problems of substandard antimalarial products circulating within the drug distribution chains in the African region (Charles and Clive,2003).Based combination therapies are at an early stage in Africa and there is a need for extensive post-marketing surveillance(Sivong et al,2009). In Nigeria in vitro bioequivalence study of nine brands of artesunate tablets showed a significant variation in different brands (Esimonea et al, 2008; Odunfa et al, 2009). Drug market today places clinicians and pharmacists in a difficult situation regarding choice of a suitable brand and lead to spreading of counterfeit and substandard drugs in the market .In Sudan a report on the post-marketing surveillance of the various brands of anti malarial drugs-(chloroquine tablets and injections, artemether injections, quinine injections and mefloquine tablets) showed a significant problem of substandard drugs circulating in the market, they include percentage failure ranging from 0% to 100% (Afadl, et al,2006). The pharmaceutical products of poor quality might contribute to the emergence of resistance. When patients are treated with poor-quality drugs, resulting in low bioavailability, this leads to drug sub-dose, which promotes the development of resistance. It is therefore important to consider product quality when dealing with the problem of antimalarial resistance. Treatment failure, ascribed to resistance, may also be due to low

quality of antimalarials posed a problem to malaria control, and therefore to public health. So there was a need to clarify the nature and magnitude of the problem of quality and consequently how it could be specifically addressed.

This study on the quality and stability of the artesunate drug as a part of a comprehensive survey of quality and safety of all drugs circulating in Sudanese market aims to provide indication of the nature and magnitude of the problem. It is also meant to present data on the quality of oral artesunate in Sudan.

1.2. Counterfeit/Substandard drugs

Counterfeit medicine or fake, as defined by the WHO is one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeit can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging. While the substandard product is a legally branded or generic product, it is one that does not meet international standards for quality, purity, strength, or packaging. (WHO,1999).

1.2.1.Counterfeit/substandard artemisinin derivative combination drugs

Counterfeit/substandard anti-malarial drugs were found in both public and private sectors. Although artemisinine- derivatives are relatively inexpensive compared to other synthetic drugs, this asset has been devalued by the presence of substandard production. Counterfeits have been found in several Asian countries , up to 38% of artesunate based malaria medications are counterfeit, (WHO,2003). In 2004 most African countries have changed to artemisinine derivative–based combination therapy as first-line malaria treatment (Malik et al, 2006). Shortage in artemisinines drugs provided a

favorable situation for the spread of fake artemisinines that put the live of thousands of African children at risk. There is a thriving fake antimalarial drug industry in Africa (Basco, 2004). Fakes containing sub therapeutic amounts of artesunate could result in the emergence and spread of resistance to the artemisinins drugs, shortening the useful life of these vital medicines (Newton et al, 2006). Counterfeit oral artesunate has been a major public health problem in mainland Southeast Asia, impeding malaria control (Newton et al, 2006). However, since the discovery of counterfeit artesunate in the late 1990s in mainland Southeast Asia there has been concern that much of the artesunate used by patients is counterfeit, containing no or inadequate active ingredient (Rozendaal, 2000;Newton et al, 2001;Newton et al, 2008).Public health research has neglected investigations of the quality of essential medicines, with few reliable data despite evidence suggesting that it is a major problem reducing the effectiveness of health care (Taylor et al,2001;Caudron et al,2008).There are very few reliable published estimates of the prevalence of counterfeit, substandard or degraded medicines for any country (Newton et al, 2006). Estimates of the prevalence of fake artesunate have all used 'convenience' sampling (Newton et al, 2001; Dondorp et al, 2004), which is potentially flawed by bias (Newton et al, 2009). Biases may overestimate or underestimate the prevalence of poor quality drugs depending on whether the drug collectors, consciously or subconsciously, prefer to find or not find poor quality medicines. For quantitative estimates of the prevalence of counterfeit and substandard medicines and to allow comparisons through time, a standardized randomized sampling procedure, of sufficient sample size, is needed (Newton et al, 2009).

1.3. Stability of medicinal products

A medicinal product is designed to possess certain desirable properties. When the product is administered by the specified route, the active constituent should achieve the required rate and extent of bioavailability. The product itself should be efficacious, safe, and acceptable to the patient; it should be convenient in use and stable. The stability of a product relates to its resistance to the various chemical, physical, and microbiological reactions that may change the original properties of the preparation during transport, storage, and use. Other criteria of stability are the effects of such changes on the fitness of the product for use as a medicine (Codex, 1994). Stability is often expressed in quantitative terms as the shelf-life. Shelf-life is the time during which the medicinal product is predicted to remain fit for its intended use under specified conditions of storage. The shelf-life of a medicinal product kept in its closed container under specified conditions is the time from manufacture or preparation until the original potency or content of active constituent has been reduced by 10%. This time is known as the $t_{10\%}$ (Codex, 1994).

1.3.1. Reaction kinetics

Reaction kinetics is the study of rate of chemical change and the way in which this rate is influenced by conditions of concentration of reactants, products, and other chemical species which may be present, and by factors such as solvent, pressure, and temperature. The most common types of reactions do not fit into any simple model of reaction kinetics .However most degradation process do fit to either zero- order or first -order kinetics equations (Codex, 1994).

1.3.1.1. First order reaction

The rate of a reaction (R) is proportional to the first power of the concentration of a reactant and may be expressed mathematically as follows:-

When log c is plotted against t it will gave straight line; and the values of K , t10, t1 was expressed as follows:

K = -slop x 2.303

t_{10} = 0.105/K

t_{50}= 0.693/K

1.3.1.2. Second order reaction

The rate of a reaction is proportional to concentration of each of two reactants or the second power of the concentration of one reactant and may be expressed mathematically as follow:

$- dc_A/dt = -dc_B/dt = K.c_A c_B$

t_{50} =1/K a

1.3.1.3. Zero order reaction

The rate is independent of concentration of reactants. In such cases the rate is expressed as follows:

- dc/dt =K

And t_{10}, t_{50} are expressed as follows:

t_{10} = 0.1a/K

t_{50} = 0.5a/ K

Where a is the initial concentration of a reactant. (Codex, 1994).

1.3.2. Factors affecting product stability

The stability of drug substances and dosage forms can be affected by different environmental factors such as exposure to adverse temperature, light, humidity, oxygen, and carbon dioxide. The major factors that influence drug stability include particle size, pH, solvent system composition, compatibility of anions and actions, ionic strength, primary container, specific chemical additives, and molecular binding and diffusion of drugs and excipients. There are many other reactions that cause loss of drug content such as, hydrolysis, epimerization, decarboxylation, oxidation, photochemical decomposition (Codex ,1994).

1.3.3. Testing frequency

For long-term studies, frequency of testing should be sufficient to establish the stability of the finished pharmaceutical product. The frequency of testing at the long-term storage conditions should normally be every three months over the first year, every six months over the second year and annually thereafter throughout the proposed shelf-life. At the accelerated storage condition, a minimum of three time points, including the initial and final time points , from a six-month study is recommended (WHO, 2007; WHO,2009).

1.3.4. Climatic zones

Five climatic zones can be distinguished for the purpose of worldwide stability testing, .These are:-

- Zone I: temperate climate.
- Zone II: subtropical and Mediterranean climate.

- Zone III: hot and dry climate.
- Zone IVA: hot and humid climate.
- Zone IVB: humid climate.

The WHO specified for long-term stability study at 21 ± 2°C / 45% RH for Zone I, 25 °C ± 2 °C/60% RH ± 5% RH for Zone II, 30± 2 °C / 35% RH for Zone I11,30 °C ± 2 °C/65% RH ± 5% RH for Zone IVA and 30 °C ± 2 °C/75% RH ± 5% RH for Zone IVB. The temperature for long – Term stability study is calculated from the mean kinetic temperature (WHO, 2007; WHO, 2009), which is the temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures. It is calculated from temperature in a storage facility (USP2007).

Artemisinin compounds are sensitive to moisture. The shelf-life of most products is around two years and this depends on high standards of blister-packaging and good storage (WHO, 2003). Attention must therefore be paid to their manufacturing and storage conditions. Furthermore, there is limited experience with these products by drug regulatory authorities and health care professionals. It is therefore necessary to adhere to stringent raw material standards, drug-manufacturing practices, norms and standards (Good Manufacturing Practices, GMP). The product(s) should be appropri-ately blister-packed to assure maximal stability and product integrity (WHO, 2003). The pharmacopeia monographs of artesunate tablet recom-mended storage condition for artesunate(IP,2005;Chinese pharmacypeia-,2005;Indian pharma-copeia,2009).

New artemisinin combination therapies pose difficulties of implem -entation in developing and tropical settings because they have a short shelf-

life relative to the medicines they replace (Roger et al, 2009). This limits the reliability and cost of treatment, and the acceptability of this treatment to health care workers. A multi-pronged investigation was made into the chemical and physical stability of fixed dose combination therapies stored under heterogeneous, uncontrolled African conditions, to probe if a shelf-life extension might be possible(Roger et al, 2009).Seventy samples of expired ART+LUM were collected from private pharmacies and malaria researchers in seven African countries, and subjected to thin-layer chromatography (TLC), disintegration testing, and near infrared Raman spectrometry for ascertainment of active ingredients, tablet integrity, and chemical degradation of the tablet formulation including both active ingredients and excipients. The data indicated that ART+LUM is chemically and physically stable well beyond its stated shelf-life in uncontrolled tropical conditions (Roger et al, 2009). The stability tests of the reconstituted suspensions for artesunate, dihydroartemisinin and artemether, showed bad results for artesunate, even when the pH was adapted. In contrast, dihydroartemisinin showed only 10% degradation within 10 days and artemether was stable at least 21 days. (Gabriëls and Plaizier, 2004).

Sudan as a large country with total area of about 3.5 million Km^2, possesses different climatic conditions ranging from hot and dry in the North, to hot and humid in the East, and tropic in the South. WHO classified Sudan under Zone IVA (WHO, 2009). Sudan imports drugs from various countries .The majority of these drugs are transported by sea, through the sea port at Port Sudan .However the climatic condition at the harbor in Port Sudan is very drastic especially during autumn when relative humidity is up to 65% and the maximum temperature is over 45°C. These drastic conditions may affect the stability of drugs and cause physical or

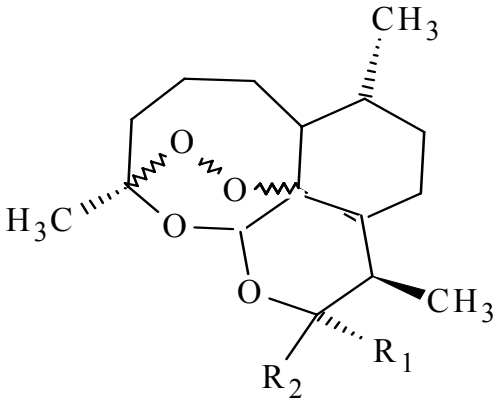
chemical changes of the drugs in Sudan. Different antimalarial and other drugs had been studied during transport and storage condition in Sudan. The results showed in-stability of the drugs upon transportation and storage at room temperature. Results of the stability study of different drugs in Sudan, showed a significant decrease in the content of the active ingredient in some pharmaceutical products including lignocaine injection, adrenaline injection, suxamethonium chloride injection, ergometrine maleate injection, ampicillin capsules, tetracycline capsules and procaine penicillin injection (Abu-Reid et al, 1990). A report on the storage and transport of ART+LUM tablets in Sudan showed un-stability of ART tablets upon transportation by the normal transport condition and storage at room temperature (Gamil et al, 2008).

Literature review showed that there is no study of the stability of artesunate in Sudan.

1.4. Artemesinin and its derivatives

Artemesinin is a Chinese herb (Qinghaosu) that has been used in the treatment of fevers for over 1,000 years, thus predating the use of Quinine in the western world (Woodrow. et al, 2005). It is derived from the plant Artemisia annua, with the first documentation as a successful therapeutic agent in the treatment of malaria is in 340 AD. The active compound was isolated first in 1971 and named artemsinin. It is a sesquiterpene lactone with a chemically rare peroxide bridge linkage. It is this that is thought to be responsible for the majority of its anti-malarial action. At present it is strictly controlled under WHO guidelines as it has proven to be effective against all forms of multi-drug resistant P. falciparum. It is only given in combination with other anti-malarials (Mankil, 1994).Various semi synthetic derivatives of artemisinin[artenimol (dihydroarte misinin), artesunate, artemether and

artemotil(arteether)] are in use for the treatment of patients with either uncomplicated or severe malaria, including multidrug-resistant falciparum malaria. (Klayman, 1985).



R_1,R_2 = O	Artemisinin
R_1= H, R_2 = OH	Dihydroartemisinin
R_1= H, R_2 = OCH_3	Artemether
R_1= H, R_2 = OCH_2CH_3	Arteether
R_1= H, R_2 = $OCH_2C_6H_5CO_2H$	Artelinic Acid
R_1= H, R_2 = $OCOCH_2CH_2CO_2H$	Artesunic Acid (artesunate)

Figure No. (1): Structures of artemisinin and its derivatives.

1.4.1. Chemistry and general properties of artemesinin and its derivatives

The chemical structure of artemisinin is quite different from all previously known antimalarials.The compound is an unusually stable sesquiterpene lactone bearing a peroxy group . The presence of the peroxide bridge is essential for artemisinins antimalarial activity as a reduced form of the compound, deoxyartemisinin, lacks the antimalarial activity. (Woerdenbag et al, 1994).

1.4.2. Mechanism of action of artemesinin and its derivatives

The specific mechanism of action of artemisinins is not well understood, and there is ongoing research directed at elucidating it. One of these postulation attributed that artemisinin contains a structural feature called a peroxide bridge, which is believed to form highly reactive free radicals. The theory has been that these artemisinin-derived free radicals chemically modify and inhibit a variety of parasite molecules, resulting in parasite death. A rich source of intracellular Fe^{2+} is haem—an essential component of haem-oglobin—and it has long been suspected thatFe^{2+}-haem is responsible for activating artemisinins inside the parasite (Robert,2003). Other sources attributed the mechanisms of action of artemisinin to interference with parasite transport proteins, disruption of parasite mitochondrial function, modulation of host immune function and inhibition of angiogenesis (Golenser et al, 2006).

1.4.3. Antimalarial efficacy of artemesinin and its derivatives

Artemisinin and its derivatives have proved effective against strains resistant to conventional antimalarials such as chloroquine and mefloquine. (Alin, et al, 1992; Price et al, 1998; Winstanley et al, 2000). There is no clinically relevant artemisinin-resistant human malaria, although there are developments of the rodent malaria parasite strains resistant to the drug (Chawira, et al 1986; Li, et al, 1989). The genetic basis of the artemisinin and its derivatives has a rapid antimalarial effect, decreasing the number of parasite faster than any other known drug (White, et al, 1994). Also lower gametocyte carriage rates have been observed after treatment with artemisinin and its derivatives (Price et al, 1996). The fast decline in the number of parasites is beneficial in combination therapies (White et al,

1999). Another advantage of the rapid clearance of the parasite is the earlier return of the patients to the normal life. However, since the clinical symptoms of malaria disappear within a day or two after treatment initiation, compliance could become a problem. The rapid decline in the number of parasites has not proved to be of clinical benefit compared to quinine in severe malaria cases (Cao et al, 1997), although there seems to be a lower frequency of side effects in patients treated with the artemisinin compounds (Tran et al, 1996).

1.4.4. Clinical safety and Toxicity of artemesinin and its derivatives

Artemisinin and its derivatives are well tolerated in clinical practice. (Dayan et al, 1998; Van et al, 2000; White and Olliao, 1998). The neur-otoxicity seen in animals after high doses of these compounds has not been reported in humans. (Ambroise,1999). The artemisinin compounds are considered to be well-tolerated, with few or none side effects in clinical use (van Agtmael et al.1999).

1.5. Artesunatum – Artesunate

$C_{19}H_{28}O_8$ (Figure 1)

1.5.1. Chemical name

(3*R*,5a*S*,6*R*,8a*S*,9*R*,*10S*,12*R*,12a*R*)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10-ol, hydrogen succinate.(IP, 1995).

1.5.2. Physical properties

Afine, white crystalline powder, very slightly soluble in water; very so-luble in dichloromethane R; freely soluble in ethanol (~750 g/l) TS and acetone R. (IP, 1995).

1.5.3. Pharmacokinetics of artesunate

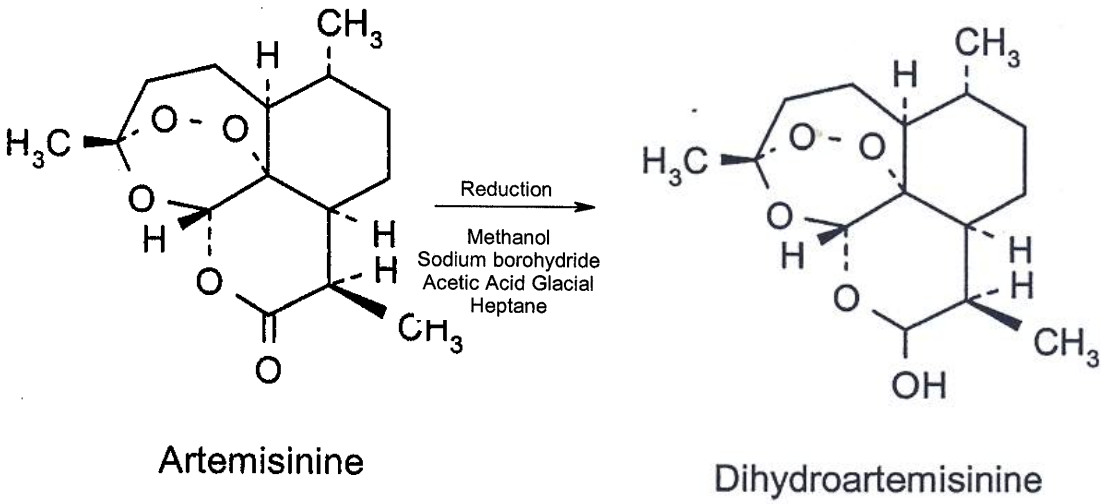
The artesunate is characterized by a short half-life and rapid action. artesunate is rapidly converted to artenimol (DHA) at rates that vary with the route of administration(Navaratnam et al, 2000). Following intravenous injection, artesunate has a peak plasma drug concentration (C_{max}) of 13.7 mg/L, an elimination half-life ($t_{½}$) of 2.2 min, a clearance of 3.0 L/hr/kg, and a volume of distribution of 0.16 L/kg. Dihydroartemisinin has a C_{max} of 2.2 mg/L, a t_{max} of 8 min, a $t_{½}$ of 37 min, an apparent clearance of 1.1 L/hr/kg, and an apparent volume of distribution of 0.9 L/kg. Following oral artesunate, the mean relative bioavailability of DHA is 85%, the C_{max} is 3.0 mM (0.85 mg/L), the t_{max} is 75 min., and $t_{½}$ was 40 min. (Benakis et al, 1998).

1.5.4. Synthesis of artesunate

There are several methods of the synthesis of artesunate . Artesunate is synthesized by the extraction of artemisinine with dichloromethane and purified on the basis of variations in polarity and in the hydrophile/lipophile balance of solvents. Transformation into artesunate was a two-step process involving reduction to dihydroartemisininee using diisobutylaluminium hydride followed by esterification using succinic anhydride. (Chekem and Wierucki S, 2007).Another method of synthesis is by the chemical modification of artesunate to the key compound dihydroartemisinin by

reduction with sodium borohydride in methanolic suspension. The hemi succinate (artesunate) was obtained by estrification of dihydro artemisinine with succinic anhydride under basic condition.(Presser and S.Buzzi. 2009). Also artesunate is synthesized by transformation into artesunate by two-step process involving reduction to dihydroartemisininee using methanolic solution of sodium borohydride and acetic acid glacial in presence of heptane followed by esterification using methylene chloride and succinic anhydride in presence of heptane Figure(2) (János,2004).

ARTESUNATE SYNTHESIS – Step1



ARTESUNATE SYNTHESIS – Step2

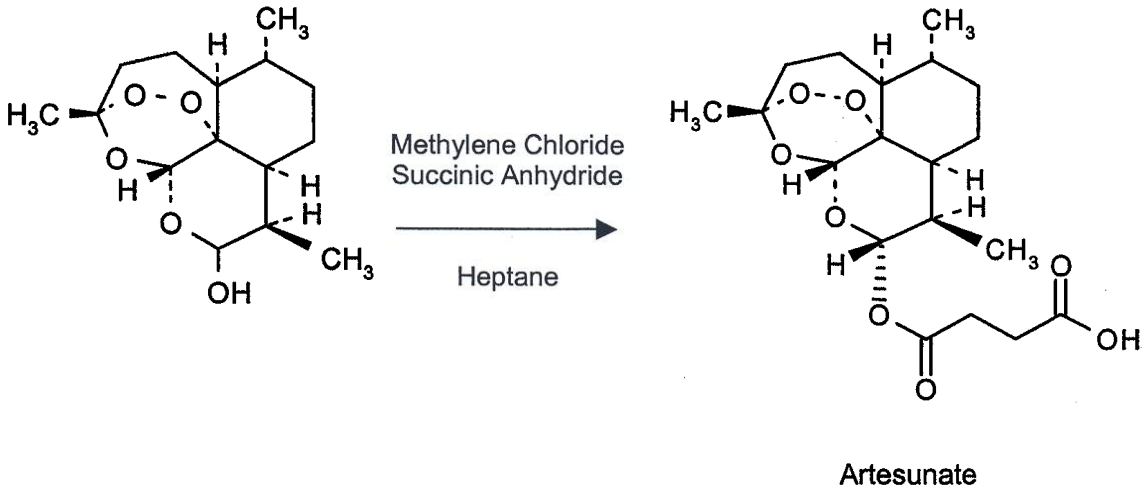


Figure No. (2): Synthesis of artesunate(Reproduced from Ref. János,2004)

1.5.5. Resistance

A potential for resistance development by Plasmodium species to artesunate was examined in vitro and in vivo. In a preliminary study, the erythrocytic forms of the FCR3 strain of P. falciparum were passaged by exposure to increasing concentrations of artesunate (starting with 4 ng/ml) for 48 hours each, followed by growth in drug-free medium for 18 days (equivalent to 9 life cycles). The artesunate IC_{50} value increased by 3-fold after 6 to 7 passages over a period of 130 days. Such an effect was reversible when the parasites were grown in drug free medium for 5 weeks.Studies in vivo show that serial passage of the N strain of P. berghei in mice treated with escalating doses of artesunate for 4 days each, increased the 90% effective dose (ED_{90}) by about 29-fold after 21 passages (85 days). The effect was reversible after discontinuation of therapy. However, the clinical significance of these observations is unknown. In patients with severe or moderate malaria, treatment with a single dose of rectal artesunate decreased the parasite count by > 90% in 24 hours. In patients treated with multiple doses of artesunate (oral, rectal or IV) the parasite clearance time was 16 to 56 hours. However, recrudescence was reported on Days 10 to 28 after discontinuation of therapy. In the absence of genotyping and phenotyping it is unclear whether the recrudescence is due to resistance. Also, the presence of dormant parasites cannot be ruled out (White.2004).

1.5.6. Drug combination

A combination of artesunate with mefloquine or quinine is synergistic against P. falciparum. However, a combination of artesunate with pyri-methamine is antagonistic. The combination of artesunate with chloroquine varied from additive to antagonistic against the different P. falciparum

strains tested. The oxidant drugs (miconazole and doxorubicin) also show a synergistic effect in combination with artesunate. A combination of artemisinin with mefloquine is synergistic whereas that with pyrimethamine is antagonistic in vitro and in vivo. Combinations of artemisinin with other antimalarials (sulfadiazine, sulfadoxine, sulfadoxine-pyrimethamine, cycloguanil, and dapsone) were also shown to be antagonistic in vivo (WHO, 2001).

1.5.7. Stability of artesunate

Amulti-prolonged investigation was made into the chemical and physical stability of artesunate and fixed dose combination (AS+AP). Artesunate was found to be stable in 0.9% w/v sodium chloride at 9°C, 23° C and 36.5° C for 130h, 10.6h and 1.6 h, respectively. Exposure to light did not affect the degradation rate; (Batty et al, 1996). Muco-adhesive gel formulation of artesunate storage in tropical climates in the dry component of the gel, showed stablility in the dry blend for 6 months at 45 °C and 60% RH. (Karen et al, 2008). Instability of artesunate was established in three pharmaceutical solvents ethanol, propylene glycol and polyethylene glycol 400 (PEG 400). None of these solvents prevented artesunate from degradation longer than 3 months (Gaudin et al, 2007).The stability tests of the reconstituted suspensions showed bad results for artesunate, even when the pH was adapted. In contrast, dihydroartemisinin showed only 10% degradation within 10 days and artemether was stable for at least 21 days (Gabriëls and Plaizier, 2004). Artesunate drug substance, for a rectal capsule formulation, when heated at 100 °C for 39 h gives β-artesunate, artesunate dimers, 9,10-anhydrodihy-droartemisinin (glycal), a DHA β-formate ester, and smaller amounts of other products that arise via intermediate formation

of dihydroartemisinin (DHA) and subsequent thermal degradation.(Richard et al,2007). WHO reported the effect of the humidity on artesunate tablets and recomended blister-packed for artesunate tablets (WHO, 2003). Also the pharmacopeias recommended different storage conditions for artesunate tablet:

Artesunate tablets should be kept in a well-closed container (Chinese pharmacopeia, *1996),*
Artesunate tablets should be kept in a well-closed container, protect from light(IP,2005).
Artesunate tablets should be kept in a well-closed container (IP2009).
Store protected from moisture (Indian pharmacopeia.2009).
Packaging in tightly closed, light-resistant container at temperature not exceeding 30° (USP, 2009).

1.5.8. Assay of artesunate

Several analytical methods are now available for determination of artesunate in pharmaceutical dosage form and in biological fluid. A simple spectrophotometric method for the determination of artesunate is described; the method is based on the reaction of H_2O_2 generated by the cleavage of endoperoxide linkage of artesunate and its reaction with potassium iodide to liberate iodine. The liberated iodine bleaches the red colored Safranin O to colorless species and is measured at 521 nm while it oxidizes color-lessVariamine blue to violet colored species and is measured at 556 nm (Thekke and Badiadka, 2009). A reversed phase liquid chromatographic method was developed for the simultaneous determination of artesunate and amodiaquine in combined pharmaceutical dosage form , chromatographic separation of the two drugs was performed on a BDS Hypersil C18,

100 mm × 4.6 mm, 3 μm particle size column as stationary phase with a mobile phase comprising phosphate buffer (pH 3.0) and acetonitrile in the proportion of 50:40 (v/v), at a flow rate of 0.8 mL min−1 and UV detection at wavelength 210 nm for artesunate and 300 nm for amodiaquine using photodiode array detection.(Manishaet al,2008).HPTLC method has been developed for the estimation of artesunate in bulk and pharmaceutical formulations. The study employs silica gel F_{254} as stationary phase on aluminium foil and mobile phase comprising toluene: ethyl acetate: acetic acid (2:8:0.2). Vanillin (1%) in sulphuric acid (5%) in ethanolic solution gave prominent well-resolved pink colour spot for artesunate, which was stable for more than a day. The densitometric analysis was carried out in the absorbance mode at 520 nm.(Agarwal, et al,2007). Also High-performance liquid chromatography has been developed for artesunate tablet , using a stainless steel column (10 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (3 μm) and a mixture of 44volumes of acetonitrile and 56 volumes of buffer pH 3.0 as the mobile phase. The system operates with a flow rate of 1.0 ml per min. (Ema, 2009). Artesunate was analysed by liquid chromatography with atmospheric pressure chemical ionisation (APCI) mass spectrometric (MS) detection on a Hypersil Gold column (100 mm x 4.6 mm) using a mobile phase containing methanol-ammonium acetate 10 mM pH 5.3 (70:30, v/v) at a flow rate of 1 mL/min.(Lindegårdh, 2007). A high-performance liquid chromatographic method with reductive electrochemical detection is described for the simultaneous quantification of artesunate and dihydroartemisinin (DHA) in plasma. The procedure involved the extraction of artesunate, DHA and the internal standard (artemisinin) with a mixture of dichloromethane and tert.-methyl butyl ether (8:2, v/v). Chromatographic separation consisted of the mobile phase (acetonitrile–water containing 0.1

M acetic acid, pH 4.8; 45:55, v/v) running through the column (Nova-Pak C18, 150 cm×3.9 mm I.D., 5μm particle size) (Bangchang et al, 1998). In support of the development of specifications, major impurities are identified using high resolution HPLC–MS, isolation via preparative HPLC followed by NMR. The identified impurities differ from those previously claimed (Rodger et al, 2009). Also sensitive method has been developed for the determination of artesunate and its active metabolite dihydroartemisinin (DHA) in human plasma using artemisinin as an internal standard. Solid phase extraction using Oasis HLB extraction cartridges was used for sample preparation and analysis was performed on a Shimadzu LCMS-2010 in single ion monitoring positive mode using atmospheric pressure chemical ionization as an interface. Positive ions were measured using extracted ion chromatogram mode. The extracted ion for artesunate, α- and β-DHA was m/z 221 and for artemisinin was m/z 283. Chromatography was carried out using a Synergi Max-RP, 4 μ, 75 mm x 4.6 mm column using glacial acetic acid 0.1%, acetonitrile and methanol mixture (38:46.5:15.5) as a mobile phase delivered at a flow rate of 0.5 mL/min. (Himanshu et al, 2005). Also other method was developed to analyze human plasma samples for the contents of artesunate and dihydroartemisinin. The plasma samples are extracted with ethyl acetate, concentrated, and redissolved in water/acetonitrile. Analysis was performed with liquid chromatography-mass spectrometry using a binary gradient program with aquaeous formic acid and acetonitrile formic acid on a XTerra MS C18-column. (Van et al, 2008). Liquid chromatography-mass spectrometry (LC-MS) analytical method used for the co-quantification of artesunate and its active metabolite, dihydroartemisinin in human plasma using artemisinin as an internal standard. The liquid-liquid extraction of samples was carried out using dichloromethane and tert.-methyl butyl ether (at a ratio of 8:2v/v) and then

evaporated to dryness by a stream of nitrogen gas at room temperature. Chromatographic separation and mass analysis were performed on chromatography/mass spectrometer detector trap system, using electrospray ionization as an interface. The stationary phase was an Elipse XDB-C18 column. The mobile phase contained acetonitrile and 0.003 M glacial acetic acid at ratio of 62:38(v/v) delivered ataflow rate of 0.5ml/min.(Lindegardh et al,2009)

Pharmacopeial monographs published different methods of analysis of artesunate in bulk and in dosage formulations. Chinese pharmacopeia (1996) published titration methods by dissolving an accurately weighed quantity of powder containing about 0.5g of artesunate in 50 ml of neutralized ethanol and phenolphthalein/ethanol TS as indicator. IP2005 published an HPLC method using stainless steel column (12.5cm×3mm) (5µ) C18, a mixture of equal volumes of acetonitrile and buffer (potassium dihydrogen phosphate pH 3.0) as mobile phase, flow rate 0.6 ml per minute, and UV-detector set at 216 nm. Also IP published a draft in 2009 changed the previous HPLC method of the assay to anther HPLC method using stainless steel column (10 cm × 4.6 mm) (3 µm) C18 at 30°, mobile phase of a mixture of 44volumes of acetonitrile and 56 volumes of potassium dihydrogen phosphate (pH 3.0), flow rate 1ml per min, and UV-detector set at 216 nm .The IP(2009) method is the same as that published by Ema (2009). USP(2009) published a draft for the assay of artesunate tablets using a mixture of acetonitrile and buffer pH3 as mobile phase, column 25 cm x 4.6 mm packed with octadecylsilane bonded to porous silica 5 µm, at temperature 30°,and UV-detector set at 216 nm. Indian pharmacopeia (2009) published an assay method of artesunate tablets using HPLC method a mixture of 30 volumes of a solution of pH 5.5 (containing 3.85 g of ammonium acetate and 1 ml of triethylamine in 1000

ml of water) and 70 volumes of methanol as mobile phase, stainless steel column 15 cm x 4.6 mm packed with octadecylsilane bonded to porous silica (3.5 µm) at 15°C, flow rate 0.6 ml per min., and UV-detector set at 216 nm.

There are different Pharmacopeial methods for the dissolution test of the artesunate tablets. Unfortunately, these official methods have their demerits which greatly impair their functionality specialy in developing countries like Sudan .It is either a problem of non- availability of equipment needed for the assay procedure (IP2009;Indian pharmacopeia 2009),or non sensitivity of the method (Chinese pharmacopeia 1996;USP,2009). IP (2009) published a draft of the dissolution test for solid oral dosage form using buffer pH 6.8 as dissolution medium, paddles, and 75rpm for 45 minutes. After that the samples are filtered through in-line filter and analyzed by high-performance liquid chromatography, using a stainless steel column C18 (25cm × 4.6 mm) (5µm) at 30°C, a mixture of equal volumes of acetonitrile and buffer pH 3.0 as mobile phase, flow rate 1.5 ml per minute, and UV-detection at λ_{max}210 nm. Indian pharmacopeia (2009) published a method for the dissolution test using apparatus No. 1, phosphate buffer pH 5.0 as dissolution medium, and the system rotation at 50 rpm for 30 minutes. The chromatographic system consists of stainless steel column C18 (15cm x 4.6mm) (3.5 µm) at 15°C, a mixture of 30 volumes of a solution of pH 5.5 (containing 3.85 g of ammonium acetate and 1 ml of triethylamine in 1000 ml of water) and 70 volumes of methanol as a mobile phase. The flow rate is 0.6 ml per minute, and the samples are analyzed by UV-detector at 216 nm. Chinese pharmacopeia (1996) and USP (2009) published the same method of the dissolution test, using apparatus 1, distilled water as a dissolution medium, and rotation speed at 100 rpm for 30min.The samples are analyzed using UV-Spectrophotometer at λ_{max}289nm.

1.6. Quality assurance of pharmaceutical products

Quality assurance of pharmaceutical products is assurance of the quality, safety and efficacy of pharmaceutical product. It is a continuing concern of WHO. Despite efforts made around the world to ensure supply of high-quality and effective drugs, substandard, spurious and counterfeit products still compromise health care delivery in many countries (WHO, 2003). To respond to the global need for adequate quality assurance of pharmaceuticals, WHO has over the years made numerous recommendations to establish standards and guidelines to promote the effective functioning of national regulation and control systems and the implementation of internationally agreed standards by trained personnel (WHO, 2004). This is an initiative through which WHO, in collaboration with other UN agencies, will pre-qualify manufacturers of artemisinine compounds and ACTs on the basis of compliance with internationally recommended standards of manufacturing and quality (WHO,2003).Dr Ying1998 (Shanghai Institute of Materia Medica of the Chinese Academy of Sciences) asserts "If local drug regulators in developing countries are not equipped with easily portable, operable and low-cost analysis equipment, it is still very difficult for them to effectively and efficiently prevent fake drugs against malaria.

1.6.1. Quality of pharmaceutical products

The suitability of drugs for their intended use is determined by their efficiency weighed against safety, according to label claim, or as promoted or publicized and their conformity to specifications regarding identity, purity and other characteristics (WHO, 2009). It is a concept that covers all measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that the raw materials, intermediates,

packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics. Poor manufacturing practices, poor storage of a product as well as the use of incorrect excipients will lead to poor dissolution profiles and thus result in compromised bioavailability. Dissolution testing for pharmaceutical products in tablet and capsule form is required by the US Food and Drug Administration (FDA) and increasingly used outside the USA to report on the quality of drug (Obinna et al, 2009).

1.7 Method development and validation processes

The steps of methods development and method validation depend upon the type of method being developed. However, the following steps are common to most types of projects:

- Method development plan definition.
- Background information gathering.
- Laboratory method development.
- Generation of test procedure.
- Methods validation protocol definition.
- Laboratory methods validation.
- Validated test method generation.
- Validation report.

A well-developed method should be easy to validate. A method should be developed with the goal to rapid test preclinical samples, formulation prototypes, and commercial samples. As the methods development and validation processes advance, the information gathered is captured in the design and subsequent improvement of the method. The

validation protocol should be written only following a thorough understanding of the method's capabilities and intended use. The validation protocol will list the acceptance criteria that the method can meet. Any failure to meet the criteria will require that a formal investigation be conducted. The required validation parameters depend upon the type of analytical method. Pharmaceutical analytical methods are categorized into five general types (ICH, 2000):

- Identification tests.
- Potency assays.
- Impurity tests: quantitative.
- Impurity tests: limit tests.
- Specific tests.

Validation requirements depend upon the type of test method, including:

- Specificity: ability to measure desired analyte in a complex mixture.
- Accuracy: agreement between measured and real value.
- Linearity: proportionality of measured value to concentration.
- Precision: agreement between a series of measurements.
- Range: concentration interval where method is precise, accurate, and linear.
- Detection limit: lowest amount of analyte that can be detected
- Quantitation limit: lowest amount of analyte that can be measured
- Robustness: reproducibility under normal and variable laboratory conditions.

Only specificity is needed for an identification test. However, the full range of specificity, accuracy, linearity, range, limit of detection (LOD),limit

of quantitation (LOQ),precision, and robustness testing is needed for more-complex methods such as quantitative impurity methods(USP,2007; FDA,2000).

1.7.1. Developing a new dissolution method

Dissolution data based on a discriminating and well thought dissolution test is of tremendous value in the selection of the proper formulation .The dissolution test can also serve as routine control mechanism to assure the uniformity of regular production batches (Remington, 2005). Development of the new method needs the proper choice of the apparatus. There are three types of the apparatus described in the compendia, the basket, the paddle and the flow-through cell. Apparatus differ with regard to the shape and geometry of dissolution vessel, the type and intensity of agitation, the position of the dosage form, the dispersion of particles, the volume of the dissolution medium, the ability to change the solvent at a certain rate to maintain sink conditions, and the reproducibility of the system (Remington, 2005).The paddle is now the apparatus of choice for many preparations. The flow –through cell may be more appropriate for preparations of poorly soluble active ingredient (BP,2005).The medium of 900 ml of distilled water with an agitation speed of 100rpm for the rotating basket and 50 rpm for the paddle method are generally used ,the system set at 37ºC. A check to determine if dearation of water is necessary has to be conducted. If such parameters prove to be in adequate, slightly lower and higher stirring rate may be tried. If not successful, the composition of the dissolution medium could be changed. Dilute hydrochloric acid or buffer systems of different pH could be used. The tests can be conducted for various durations from 15 minutes to 24 hours with appropriate sampling.

The results of the dissolution analysis are reported as cumulated percent drug dissolved at specified time intervals (Remington, 2005).

1.8. Drug dissolution testing

Drug dissolution testing is a quantitative analytical technique for assessing drug release from pharmaceutical products, in particular solid oral dosage forms such as tablets and capsules (Remigton, 2005). The drug dissolution is critical for drug absorption into the systemic circulation (bloodstream) or human body in general. The availability of drug in the body is known as bioavailability and is defined as, the rate and extent of absorption of a drug into the systemic circulation. The rate and extent of drug absorption are generally represented by maximum observed concentration (C_{max}) of a drug in blood and area under the drug concentration versus time curve (AUC), respectively (Remigton, 2005).The drug dissolution results are compared these in vivo parameters. Describing and comparing these in vitro and in vivo relationships of drug release are referred to as in vitro-in vivo correlations (IVIVC) and are conceptually valid and widely accepted (Remigton ,2005).

Dissolution is the process by which a solid solute of only fair solubility characteristics enters into solution (Remington 2005).The rate of dissolution of solid substances is determined by a very thin layer saturated solution that forms instantaneously around the solid particles. The mathematical relationship that correlates the dissolution rate to the solubility gradient of the solid (Remington 2005) is as follows:

$$\frac{dc}{dt} = K(C_s - C_t) \qquad (1)$$

Where, dc/dt = dissolution rate of the drug

K = the proportionality constant

C_s= the saturation concentration (maximum solubility)

C_t= concentration at time t

$C_s - C_t$= concentration gradient

The proportionality constant K is also called the dissolution constant and the equation has been shown to obey first order kinetics. Eq 1 was modified to incorporate the surface area, S, as a separate variable (Remington 2005).

$$\frac{dc}{dt} = K_1 S(C_s - C_t) \qquad (2)$$

The called film model theory (Remigton, 2005) proposed that under the influence of no reactive or chemical forces, a solid particle immersed in a liquid, undergoes two consecutive steps; first is the solution of the solid at the interface, forming a thin stagnant layer or film, h, around the particle; and second, is the diffusion from this layer at the boundary to the bulk of the fluid. The first step (solution) is almost instantaneous, the second (diffusion) is much slower and therefore, is the rate limiting step, Eq 2 was expanded to include the diffusion coefficient, D, the thickness of the stagnant diffusion layer, h, and the volume of the dissolution medium, v, producing Eq3(Remington,2005).

$$\frac{dc}{dt} = K_2 \frac{DS}{vh}(C_s - C_t) \qquad (3)$$

1.8.1. Sink condition

The term sink condition originated from a fact that the drug concentration on both sides of the epithelial layer of the intestinal wall approaches equilibrium in a short time, and that the gastrointestinal tract acts

as a natural sink; i.e., the drug is instantaneously absorbed the moment it dissolves (Remington 2005). Therefore, under in vivo conditions, there is no concentration buildup and hence the retarding effect of the concentration gradient on the dissolution rate, as predicted by Eq 1, does not occur. In order to simulate the in vivo sink condition, in vitro dissolution testing is usually conducted using either a large volume of dissolution medium or a mechanism by which the dissolution medium is constantly replenished with fresh solvent at specified rate so that the concentration of the solute never reaches more than 10–15% of its maximum solubility. If such a parameter is maintained, the dissolution testing is said to be conducted under sink condition, as seen from the following mathematical treatment. Assuming Cs >> Ct, Eq 3 becomes,

$$\frac{dc}{dt} = K_2 \frac{DS}{vh} C_s \qquad (4)$$

As C_s and D are constants for each specific chemical substance therefore they could be incorporated in K_2 and Eq 4 becomes,

$$\frac{dc}{dt} = k_3 \frac{S}{vh} \qquad (5)$$

If the volume of the dissolution medium, the surface area and the thickness of the stagnant diffusion layer (h) are kept constant during the duration of the dissolution test, then

$$\frac{dc}{dt} = K \qquad (6)$$

Eq. 6 predicts a constant dissolution rate under sink condition and represents a zero order kinetic process, i.e. the concentration of the drug increases linearly with time. Eq 6 is also believed to approximate the in vivo condition where the dissolution rate of sparingly soluble drugs plays a

fundamental role in determining their bioavailability. In Eq 2, the surface area was considered constant for the duration of the dissolution test. Although this could be achieved, by using a non disintegrating disk of the chemical substance, a technique usually employed for the determination of the intrinsic dissolution rate, the same could not be maintained for a dissolving crystal or regular solid dosage form where complete disintegration is a priority. To develop a dissolution equation that is based on a changing surface area ,Eq 2 was modified to represent the rate of appearance of the solute in the solution by multiplying each side of the equation by v (volume), letting

$$k_2 v = K$$

$$\frac{dW}{dt} = KS(C_s - C_t) \qquad (7)$$

Where W is the weight of solute in solution.

Also by assuming that S = $kw^{2/3}$, where k is a constant containing the shape factor and the density of the particle, and w is the weight of un dissolved particles at time t,

$$\frac{dw}{dt} = K(kw^{2/3})\ (C_s - C_t) \qquad (8)$$

After multiple mathematical treatments involving the application of Fick's first law and integration under the condition that W is equal to W□ , the weight of the particle at time zero ; Eq (9) result ,

$$w_o^{1/3} - w^{1/3} = K^1 t \qquad (9)$$

Eq (9) is called the Hixson and Crowell's Cubic Root Law for dissolution (Remington 2005).

1.8.2. Factors affecting the rate of dissolution

There are three factors that affect the rate of dissolution (Remington 2005).

1.8.2 .1. Factors relating to the physicochemical properties of the drug

The physicochemical properties of the drug substance play a prime role in controlling it's dissolution from the dosage form (Remington,2005).The aqueous solubility of the drug is the major factor which determines it’s dissolution rate. Other factors that affect the dissolution rate include particle size, crystalline state, such as polymorphism and state of hydration, solvation, complexation, as well as surfactant and other reactive additive. Other physicochemical propertiess such as density, viscosity, and wettability contribute to the general dissolution problems of flocculation, flotation and agglomeration. Adsorption characteristics of the drug have also been found to have a significant effect on the dissolution of certain drugs. (Remington 2005).

1.8. 2.2. Factors relating to the solid dosage form

These include:

1.8.2.2.1. Effect of formulation factors

The dissolution rate of a pure drug can be altered significantly when mixed with various adjuncts during the manufacturing process of solid dosage forms. These adjuncts are added to satisfy certain pharmaceutical functions such as diluents (fillers), dyes, binders, granulation agents, disintegrants, and lubricants (Remignton, 2005). Identical tablet and capsule products manufactured by different pharmaceutical factories were found to

exhibit significant difference in dissolution rates for their active ingredients (Remington, 2005).

1.8.2.2.2. Effect of the processing factors

The many processing factors used in tablet manufacturing greatly influence the dissolution rates of the active ingredients. The method of granulation, the size, density, moisture content and age of the granules, as well as the compression force utilized in the tabletting process, all contribute to the dissolution rate characteristics of the final product (Remington, 2005).

1.8.2.2.3. Effect of compression force on dissolution rate

There is great influence of the compression force employed in the tabletting process on the apparent density, porosity, hardness disintegration time, and average primary particle size of compressed tablets (Remington, 2005). There is always a competing relationship between the enhancing effect due the increase in surface area through the crushing effect and the inhibiting effect due to the increase in particle bonding that causes an increase in density and hardness and, consequently, a decrease in solvent penetrability. The high compression also may inhibit the wettability of the tablet due to the formation of a firmer and more effective sealing layer by the lubricant under the high pressure and temperature that usually accompanies a strong compressive force (Remington, 2005).

1.8.2.3. Factors relating to test parameters

These include, intensity of agitation, temperature, selection of the dissolution medium, surface tension and viscosity of the dissolution medium (Remington, 2005).

1.9. Quality testing technique

Recent progress in methods development is largely a result of improvements in analytical instrumentation. This is especially true for chromatographs and detectors. Isocratic and gradient reverse-phase HPLC have evolved as the primary techniques for the analysis of nonvolatile active pharmaceutical ingredients (APIs) and impurities. The HPLC detector of choice for many types of methods developments the photodiode array (PDA) detector because it can be used for both quantitative and qualitative analysis. The use of a PDA detector to determine peak purity of the active ingredient in stressed samples greatly facilitates the development of stability-indicating assays. The emphasis on identification of trace impurities and degradants has led to the increased use of techniques such as liquid chroma -tography–mass spectrometry (LC–MS) and liquid chromatography–nuclear magnetic resonance spectroscopy (LC–NMR). This trend will continue with the need to better define degradation pathways. The ultraviolet (UV) absorbance detector remains the most common HPLC detector for potency and impurity determination. Once specificity has been demonstrated, the PDA detector is replaced with a variable wavelength detector and the HPLC effluent is monitored at fixed wavelengths. Stability-indicating methods often are required to measure analytes within a wide concentration range. For example, process impurities and/or degradation products may be present at levels of 0.1%, and the main active ingredient typically is present at the nominal concentration (100%).This amount is well within the linear range of a fixed wavelength detector but not within that for LC–MS detectors. Recent FDA and ICH guidance about chiral drug products and impurities has posed new challenges for methods development scientists (ICH, 2000). Recent advances in the use of chiral HPLC columns have greatly facilitated progress

in this area. The advances are primarily a result of the introduction of chiral stationary phases (CSPs) prepared by reacting amylose or cellulose derivatives with silica. The new CSPs allow trace levels of enantiomeric impurities to be measured. Gas chromatography remains the method of choice for the analysis of volatile compounds. Gas chromatography with mass spectrometry detection (GC–MS) is increasingly being used to identify impurities and determine active ingredient peak purity in stressed samples. Advances in the use of non destructive infrared (IR) and near-infrared spectroscopy (near IR) and NMR techniques are particularly promising for methods development scientists. (Jay et al, 2003).

Chapter 2

Aim & Objectives

2.1. Aim

The main purpose of this study is:-

To assess the quality of artesunate tablets in Sudan, it is a part of a comprehensive study to test the quality of antimalarial drugs in Sudanese market (post- marketing surveillance).

2.2. Objectives

1. To conduct a post-marketing surveillance of different artesunate formulations used in Sudan.
2. To assess the effect of the transport and storage conditions, at different parts of Sudan, on the stability of artesunate tablets.
3. To adopt an HPLC dissolution test method suitable for evaluating the artesunate drug release and to validate the results obtained in the field by U.V spectrophotometric method of Chinese Pharmacopeia 1996.

2.3. Research questions

1. Do a storage conditions throughout Sudan affect stability of artesunate tablets?
2. Do transport conditions throughout Sudan affect stability of artesunate tablets?
3. Do all artesunate tablets present in Sudanese market conform to the standards of quality?
4. Does the adopted dissolution method has advantages over the official Chinese Pharmacopeia 1996?

Chapter 3

Methodology

3.1. Instrumentation

- A double–beam UV-VIS spectrophotometer, Shimadzu, Japan, model 700 was used in the quantitative analysis of dissolution test. The absorption spectra of test and reference solution were recorded in 1-cm quartz cells at λ_{max} 289.

- Dissolution tester, Shimadzu, Japan, model 1700 was used in the dissolution test, using 1 liter vessel at100rpm and at37° for 30min.

- High performance liquid chromatography used was Shimadzu, Japan, connected to a UV/VIS detector SPD-10AVP with soft ware .The separations were performed at room temperature. the samples were introduced through basket I injector with 20µl sample loop.

- High performance liquid chromatography used was Varian Proster, Australia, connected to a UV/VIS detector 325and, with soft ware .The separations were performed at room temperature. The samples were introduced through basket injector with 20µl sample loop.

3.2. Columns used

- Waters-Nova pak®C18- 3µ -150mm×3.5mm was used for the stability studies.

- En.ert Sil ODS-3µ-10cm×4.6mm was used for detection of the artesunate impurities and development of the new dissolution method.

3.3. Reagents and standards

All reagents used were of analytical grade (sodium hydroxide, potassium dihydrogen phosphate, phosphoric acid, acetone, Na lauryl sulphate and acetonitrile) from BDH, Pool, England.

Distilled water from NDQCL used for dissolution test.

Cellulose filter 0.45µ PTFE membrane filter (Pall corporation ,Ann Arbor.MI,USA) used for filtration of mobile phase and samples filteration.

Artesunate working standard, Dafra Pharma ,Belgium. Batch No-ARSU-AS-106258; expiry date April/2006, and potency 99.8%.

Artesunate working standard, Shangahai-Sudan Pharmaceutical, CO. Ltd, Sudan. Batch No.20060703; manufacture date July/2006, expiry date June/2009, and potency 100.85%.

Dihydroartemisinine working standard, Shangahai Pharmaceutical, CO. Ltd, Sudan. Batch No.100202; manufacture date February/2004-, expiry date February /2009.

Artemisinine working standard, Shangahai Pharmaceutical,CO. ,Ltd, Sudan.. Batch No.100184; manufacture date February/2004-, expiry date February /2009.

3.4. Samples selected to be analyzed

Different batches of the artesunate tablets (AS+SP) from different brands circulating in the Sudanese market were collected in the post – marketing surveillance, include the following:-

- Artesumine tablets (100mg and 50mg artesunate): Guilin Pharmaceutical co., Ltd, China.
- Artecosp tablet (100mg and 50mg artesunate): Guilin Pharmaceutical co., Ltd, China.
- Ariplus tablets (100mg and 50mg artesunate): Dafra Pharma ,Belgium.
- Artemal tablets (100mg and 50mg artesunate): Lachif Pharm, Italy.
- Combisunate tablets (100mg artesunate): Ajanta Pharma limited, India.
- ASP tablets (100mg and 50mg artesunate): working standard, Shangahai Pharmaceutical, CO.,Ltd, Sudan..

Batches of artesunate tablet analyzed for stability study included:-

- Artesumine adult tablets, labeled to contain 100mg artesunate per tablet:-

Batch No .040801(manufactured date 8.2004 and expiry date 8.2007).

Batch No .041201(manufactured date 12.2004 and expiry date 12.2007).

Batch No .LS060301 (manufactured date 2.2006 and expiry date 2.2009).

Batch No .LS060401 (manufactured date 4.2006 and expiry date 4.2009).

Batch No .LS060602 (manufactured date 6.2006 and expiry date 6.2009).

- Artesumine children tablets labeled to contain 50mg artesunate per tablet:-

Batch No.040801 (manufactured date 8.2004 and expiry date 8.2007).

Batch.No.040901 (manufactured date 9.2004 and expiry date 9.2007).

Batch No. LS061201 (manufactured date 8.2006 and expiry date 8.2009).

Batch No. LS060401 (manufactured date 4.2006 and expiry date 4.2009).

Batch No. LS060601 (manufactured date 6.2006 and expiry date 6.2009).

- Artecosp adult tablets labeled to contain 100mg artesunate per tablet:-

Batch No.051106 (manufactured date 11.2005 and expiry date 11.2007).

Batch No.05021 (manufactured date 10.2005 and expiry date 10.2007).

- Artecosp children tablets labeled to contain 50mg artesunate per. tablet:-

Batch No.051018 (manufactured date 10.2005 and expiry date 10.2007).

Batch No.051020 (manufactured date 11.2005 and expiry date 11.2007).

- Ariplus adult tablets labeled to contain 100mg artesunate per tablet:-

Batch No.04Jo6 (manufactured date 8.2004 and expiry date 8.2006).

Batch No.04J11 (manufactured date 11.2004 and expiry date 11.2006).

- Ariplus children tablets labeled to contain 50mg artesunate per tablet:-

Batch No.04J22 (manufactured date 9.2004 and expiry date 9.2006).

Batch No.04ko4 (manufactured date 9.2004 and expiry date 9.2006).

- Artemal adult tablets labeled to contain 100mg artesunate per tablet:-

Batch No.F0278 (manufactured date 4.2005 and expiry date 4.2008).

Batch No.F0622 (manufactured date 7.2005 and expiry date 7.2008).

- Artemal children tablets labeled to contain 50mg artesunate per tablet:-

Batch No.E1025 (manufactured date 10.2005 and expiry date 10.2008).

Batch No.E1041 (manufactured date 12.2005 and expiry date 12.2008).

Batch No.08051 (manufactured date 6.2008 and expiry date 6.2011).

- ASP adult labeled to contain 100mg artesunate per tablet:-

Batch No.060624 (manufactured date 6.2006 and expiry date 6.2008).

Batch No.060523 (manufactured date 6.2006 and expiry date 6.2008).

- ASP children tablets labeled to contain 50mg artesunate per tablet:-

Batch No.060806 (manufactured date 6.2006 and expiry date 8.2008).

Batch No.060610 (manufactured date 6.2006 and expiry date 8.2008).

Batch No.091002 (manufactured date 1.2009 and expiry date 10.2012).

3.5. Study design and sampling

Three procedures were used for the evaluation of Stability of artesunate tablets:

- For post-marketing surveillance, several batches of artesunate tablets were collected from Northern, Eastern, Western and Central of Sudan are presenting all Sudanese market. Samples were collected randomly. Facilities which were monitored included community and hospital pharmacies, drug stores, public pharmacy and pharmacies run by mission and other non-governmental organizations (NGOs).The Collection of the samples was from four regions in Sudan (Khartoum,

Elobied , Elgadarif and Atbara) .The region from which the samples were collected were recommended by The National Malaria Control Program (NMP) in Sudan. Official inspectors (pharmacists from NMP) were coordinating the collection from several states and were responsible for sample coding and transport to the NDQCL Khartoum for analysis. Informations that were obtained with each sample included the name of the drug (trade and generic), strength, dosage form, batch number, date of manufacture, date of expiry, description of packaging material, any remarks on storage, location of samples, collection point, and date of sample collection. The study was carried out for three years every 6 moths defined as(round 1,2,3,4,5,6). Due to some problems in collection of the samples round four in Elgadarif was not included.

- Three batches of Artesumine tablets for adults (100mg artesumine)and three batches of Artesumine tablets for children (50mg artesumine) were collected by NMP inspector from the company store before dispensing, The collected samples were stored on shelves at room temperature in different regions of Sudan (Elobied ,Port Sudan, Atbara, and Khartoum) to represent West ,East, North, Center of Sudan. These also represent different climatic conditions in Sudan. According to the literature review, that artesunate tablets were found to be affected by moisture and temperature (WHO, 2003; Chinese Pharmacopeia, 2005 and IP, 2005), Elobied, Port Sudan, and Khartoum were chosen, because they are humid and hot zones. Atbara is less humid than these areas but very hot. The importation of most drugs in Sudan is through sea port area. Un-loading process and waiting usually take considerable time, and as Port Sudan is the main

Sudanese port area, it was a target for the study. The South of Sudan, though very humid through the year (tropic conditions) was unfortunately not included. The samples collected were tested at zero time, after 3, and then after 6, 9,12, 18, 24, and 36 months (WHO, 2007) for the content of the active ingredient, dissolution test, degradation product and physical appearance.

- Five brands of artesunate tablets from Central Medical Supply (CMS) stores and private companies were collected by NMP inspector. These artesunate tablets represent all brands registered in Sudan at the time of the study .Four batches (two batches of artesunate tablets for adult and two batches of artesunate tablets for children) were analyzed. These samples represent the imported brands (Artesumin tablets, Artemal tablets, Ariplus and Artecosp tablets) and local brands (ASP). The collected samples were stored directly after being cleared from the companies and CMS stores. They were stored in the National Drug Quality Control Laboratory NDQCL on shelves at room temperature and tested at zero time, and then after 3, 6, 9, 12, 18, 24 and 36 months to detect the quality of different brands at the same storage conditions. The samples were tested for the content of the active ingredient, dissolution, degradation product and physical appearance.

3.6. Method of analysis of artesunate tablets

Determination of potency, degradation products, detection of change in physical appearance and dissolution test were performed according to the IP (2005) and Chinese Pharmacopoeia (1996) to assess the quality of the products. The Chinese Pharmacopoeia was used for dissolution test as the

test has not been developed in the IP at the beginning of this study. The Chinese Pharmacopoeia method is a validated method, thus it has been used in this study to evaluate the results of different formulations .It is the method used by the NDQCL for evaluation of post-marketing surveillance of artesunate tablets.

3.6.1. Analysis of the active ingredient

3.6.1.1. Sample preparation

Twenty tablets were accurately weighed and powdered. A mass containing about 0.05gm of artesunate was accurately weighed and transferred to 25ml volumetric flask. Acetonitrile was added to dissolve and to adjust the volume .The solution was filtered through 0.45µfilter, and was analyzed using HPLC method (IP, 2005).

3.6.1.2. Standard preparation

About 0.05gm of pure powder of artesunate was accurately weighed and transferred to 25ml volumetric flask, dissolved in acetonitrile and adjusted to volume with the same solvent.

3.6.1.3. Phosphate buffer pH3

This was prepared by weighing 1.36g of potassium dihydrogen phosphate, transferred to 1000ml volumetric flask, dissolved in distilled water and adjusted to volume with the same solvent. The solution was adjusted to pH 3.0 with phosphoric acid.

3.6.1.4. Determination of artesunate content

The samples and the standard were analzed using HPLC method using mobile phase consist of mixture of phosphate buffer (pH3.0) and acetonitrile

in the ratio (1:1). The mobile phase was filtered. The separation was carried out using a C18 column with a flow rate 1.0ml/min., at wavelength 216nm (IP, 2005).The injection volume was 20µl.

The % content of the active ingredient=AUP of the samples/AUP of the standard x potency of the standard

Where

AUP = Area under the peak.

3.6.2. Test for related substances

1ml of sample preparation used in the assay method was transferred to 100ml volumetric flask, and diluted to 100ml with acetonitrile. This solution was injected with the sample prepared for assay preparation using the same HPLC parameters (IP, 2005).

3.6.3. Dissolution test method

Six tablets of artesunate were introduced into the dissolution vessels contain 900ml of distilled water. The system was set at 37C° using paddles with the rotational speed 100 rpm. A quantity of the dissolution medium in the different vessels were withdrawn after 30 minutes, and filtered with membrane filter having porosity of 0.45µ. 20ml of the filtered solution of each vessel was accurately measured using a volumetric pipette and transferred to six 25ml volumetric flask. 2.5ml of sodium hydroxide solution (1 mol/L) was added and the volume completed with distilled water (Chinese Pharmacopeia, 1996).

3.6.3.1. Preparation of the standard

0.01gm of pure powder of artesunate was weighed and transferred to 250ml volumetric flask. 200 ml of distilled water, and 25 ml of sodium hydroxide solution (1 mol/L) were added, then the volume was completed with distilled water. The dissolution samples and the standard preparation were warmed simultaneously in a water bath at 50 ± 1°C for 45 minutes, and cooled rapidly to room temperature. Absorbance of each solution was measured using distilled water as blank at λ_{max} 289(Chinese Pharmacopeia, 1996).

The % content of the active ingredient =Abs. of the samples/Abs. of the standard x potency of the standard

Where

Abs. = Absorbance

3.7. Adoption of the dissolution test method

The dissolution method was only official in the Chinese pharmacopeia(1996) at the beginning of this study till the end of 2009, using spectrophotometric method. Other pharmacopeias published drafts in 2009 some of them used HPLC method (IP draft, 2009) and Indian pharmacopeia draft, (2009) and others published the same Chinese pharmacopeia method USP draft (2009).The dissolution test method was adopted for the following reasons:

1- The spectrophotometric method is not stability indicating method.

2- Many steps are used after sample filtrations till the assay time.

3- The method needs to be carried out without delay during filtration of the samples, and at the detection time after cooling.

4- The heating step of the sample dissolution needs carful adjustment of temperature and time.

5- The official method of analysis of the main degredants of artesunate namely artemisinin and dihydroartemisinin is same as the method used to detect artesunate by UV-spectrophotpmeter (IP, 2005). The degredants are detected at λ_{max} 292nm ,which is close to the artesunate λ_{max} 289nm.These two wave lengths for detection of arte-sunate and the degredants(artemisinin and dihydroartemisinin)are very close, and may interfere and give false results,

6- From the data of the stability carried out for artesunate tablets in this work the main problem was found to be in tablets the dissolution. Thus it was therefore deemed important to develop sensitive method for testing dissolution.

3.7.1. Dissolution test conditions

The selection of dissolution medium is based on the solubility data and the solution state stability of the drug as a function of the pH value(USP,2007).Artesunate is very slightly soluble in water(IP,2005) and insoluble in acid(Indian pharmacopeia, 2009). Artesunate is absorbed in the stomach (Navaratnam et al 2000). Typical medium for dissolution may include, Water, dilute HCL, buffers in the physiologic pH range of 1.2 to 7.5 (USP2007) .As rtesunate is insoluble in water and acid, thus phosphate buffer pH 7.0 was used. But artesunate is slightly soluble in this buffer. A percentage of surfactant can be used to enhance drug solubility in case of

poorly soluble drugs (USP2007).Different concentrations of sodium lauryl sulphate(0.1,0.2,0.3%) were therefore added to phosphate buffer pH7.0 medium to improve aertesunate solubility. The results obtained were compared with the official Chinese pharmacopeia (1996), the close results were obtained with phosphate buffer in 0.2% sodium lauryl sulphate and at dissolution time 45min.

Validation of the method was carried out according to the validation protocol of the USP2007 and WHO 2007. Validation parameter such as selectivity, linearity, accuracy and precision (reproducibility), as well as chromatographic parameters like peak asymmetry were assessed. Four batches of artesunate tablets (three batches 100mg and one batch 50mg artesunate) and three different formulations of artesunate tablets(Artemal ,ASP, and Artesumine tablets) were used. The results obtained were compared with the Chinese Pharmacopeia (1996) method results.

3.7.2. Dissolution test of artesunate tablets by the adopted method

Six tablets of artesunate were introduced into the dissolution vessels containing 900ml of dissolution medium. The system was set at 37C° using paddles, with speed of 100 rpm. A quantity of the dissolution medium in the different vessels was withdrawn after 45 minutes, and filtered with membrane filter having porosity of 0.45µ .The samples were analyzed for artesunate content by HPLC method. The amount of the artesunate dissolved after 45 minutes is expressed as a percentage of the label claim.

3.7.2.1. Dissolution medium

This was prepared by weighing 6.805g of monobasic potassium phosphate, 1.164g of NaOH and 2gm of Na lauryl sulphate , then transferred them to 1000ml volumetric flask and 800ml distilled water was added to

dissolve. The mixture was sonicated for 30min.to complete the dissolution, then distilled water was added to complete the volume. The solution was adjusted to pH 7.0 with phosphoric acid.

3.7.2.2. Standard preparation

In case of artesunate tablets for children, 0.055 gm of artesunate working standard was accurately weighed and dissolved in 250 ml of the dissolution medium and sonicated for 15 minutes then 25ml of this solution was diluted with 100ml of the dissolution medium.

In case of artesunate tablets for adults, 0.1 gm of artesunate working standard was accurately weighed and dissolved in 250 ml of the dissolution medium and sonicated for 15 minutes then 25ml of this solution was diluted with 100ml of the dissolution medium.

3.7.2.3. Determination of the samples

The analysis of samples and the standard were carried out using mixture of 44volumes acetonitrile and 56 volumes phosphate buffer pH 3.0 as a mobile phase. The mobile phase was filtered and degassed before use .The separation was carried out using, C18 column with a flow rate 1.3ml/min., at wavelength 216nm (IP, 2005). The column temperature was maintained at ambient temperature. The injected volume was 20µl. Six samples were analyzed. The percentage content of the artesunate for each sample was calculated.

The % content of the active ingredient =AUP of the sample/AUP of the standard x potency the standard

3.7.3. Method validation:-

3.7.3.1. Chromatographic parameter:

3.7.3.1.1 Peak asymmetry

The peak tailing was assessed by the following equation:

Asymmetry factor (AF) =b/a

Where:

a = the leading half of the peak measured at 10% of the peak height.

b =the trailing half of the peak measured at 10% of the peak height.

Asymmetry range is 0.95-1.15 (David, 1999).

3.7.3.2. Validation parameters

3.7.3.2. 1. Specificity

To detect the interference of the degredants with the active ingredient, two solutions were prepared. One contained the expected degredants artemisinin and dihydroartemisinin pure powder in the dissolution medium. The other solution contained artesunate pure powder and the expected degredant artemisinin and dihydroartemisinin. The two solutions were analyzed using the adopted HPLC method.

To detect the interference of excipients with the active ingredient, three different formulations were analyzed using the adopted HPLC method and compared with those obtained by the UV- spectrophotometric method (Chinese pharmacopeia method, 1996).

3.7.3.2. 2. Linearity:

Series of artesunate (pure powder) solutions were prepared in the dissolution medium to give concentration of (40, 50, 60, 70, 80, 90,100,110,120 µg /ml).The solutions were subjected to dissolution test conditions and analyzed by the adopted HPLC method.

3.7.3.2. 3.Accuracy

Tablets (n=6) of each batch were subjected to dissolution test conditions and analyzed by the adopted HPLC method. The results were compared with UV-spectrophotometric method (Chinese Pharmacopeia method 1996) and calculated as the difference between the mean and the acceptance true value at 95% confidence level.

Calculation of standard error of the mean:-

$s.e.m = \frac{SD}{\sqrt{n}}$ (Miller and Miller,2005). Where:

S.e.m= standard error of the mean

Calculation of the t-value:-

$$\bar{x} = \frac{\sum x_i}{n}$$

Where

n = number of samples

x_I =values obtained for each measurement

$\bar{x}$ =mean of the measurements

Where (i) goes from 1 to n

$$t = \frac{\bar{x}_1 - \bar{x}_2}{s} \sqrt{\frac{n_1 - n_2}{n_1 + n_2}}$$

Where

$\bar{x}_1$ = mean of first sample of n_1 observations

$\bar{x}_2$= mean of second sample of n_2 observations

3.7.3.2. 4.Precision (Reproducibility):-

The dissolution test was carried out in two laboratories (NDQCL and the National Chemical Laboratory (NCL) Khartoum). The results were compared with UV-spectrophotometric method (Chinese Pharmacopeia method 1996) and calculated as the difference between the variance and the acceptance true value at 95%confidence level.

$$SD = \sqrt{\frac{(x_1 - x)^2}{n-1}}$$

Where

SD = standard deviation

n = number of samples

x_I =values obtained for each measurement

x =mean of the measurements

$$RSD\% - \frac{SD}{X} x100$$

Where

%RSD = relative standard deviation

Calculation of the F-value:-

$$F = \frac{SD_1^2}{SD_2^2}$$ (Miller and Miller,2005).

Chapter 4

Results and Discussion

4.1. Results of post-marketing surveillance of different brands of artesunate tablets (AS+SP.

Several batches of artesunate tablets (AS+SP) from different generic brands circulating in Sudanese markets were collected from Northern, Easter, Western and Central of Sudan. Facilities which were monitored included community and hospital pharmacies, drug stores, public pharmacy and pharmacies run by mission and other non-governmental organizations (NGOs).The Collection of the samples was from four regions in Sudan (Khartoum, Elobied , Elgadarif and Atbara) . The study was carried out for three years every 6 moths defined as(round 1,2,3,4,5,6). Two rounds had been done per year. Due to some problems in collection of the samples round four in Egadarif was not included. The collected samples were analyzed for their active content, degradation products, dissolution test, disintegration test and physical appearance according to IP2005 and Chinese pharmacopeia 2005. The results obtained are shown in tables (1-8, which is a part of tables31-53).

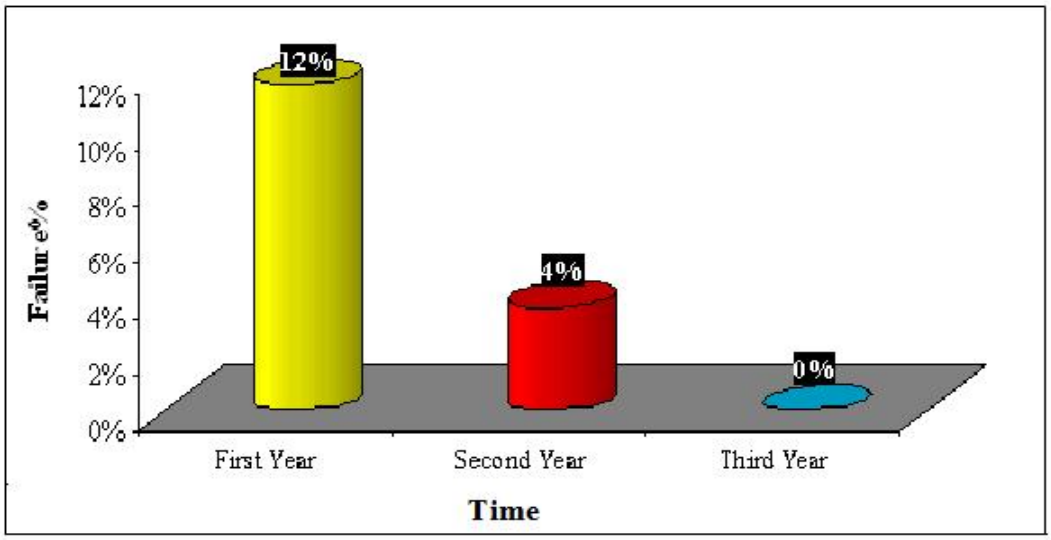


Figure No. (3): Combined percentage failure of the artesunate tablets tests in three years post- marketing surveillance

Figure (3) shows the combined results for these regions during the three years of the post-marketing surveillance, the results are expressed as a percentage of the samples failing the pharmacopoeia standards out of the total number analyzed. Failed samples were found in all regions in the first and the second year of the surveillance. The failure in the first year was 12% and in the second year was 4% and with no failure detected in the third year. The failures of the samples were in the dissolution rate, sample content and physical appearance. However there was no failure in the test of related substance for all samples analyzed. The data presented in present work indicate that there was a significant problem of substandard artesunate products circulating in the Sudanese markets, detected in the first and the second year of the study .This problem was not detected in the third year. This may be due to the action taken by the regulatory authority which removed and canceled the registration of the failed products from the market (DGP, 2007; PPRO, 2008). This action was taken as a result of a report from the present study. The results obtained from the post-marketing surveillance for artesunate tablets added specific data of substandard antimalarial drug

circulating in Sudanese markets to other published data of the substandard anti malarial drugs that carried out in Sudan by Afadl, et al,2006.Also the result obtained added general data of the substandard anti malarial drug circulating in African countries markets to other published data of the substandard anti malarial drugs that carried out in different African countries by Charles And Clive ,2003.

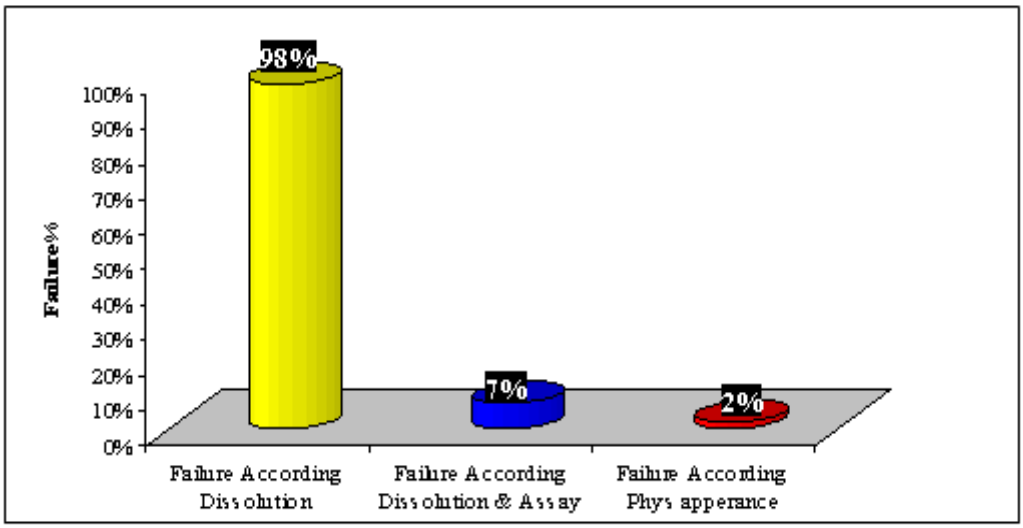


Figure No. (4): Types of failure of the artesunate tablets in three years post-marketing surveillance

Figure (4) shows the types of failure occurred to the artesunate tablets during the post marketing surveillance, expressed as percentage failure. Almost 98% failures were due to dissolution rate, followed by 7% failure due to dissolution and assay (content of the active substance), and 2% failure in the physical appearance. The data presented indicated that there is a significant problem of substandard artesunate. The most significant results were the failure in the dissolution rate. The presence of substandard artesunate products indicates a very serious problem which warrants further investigation and intervention. Nevertheless, this high rate of failure due to dissolution test indicates a very serious problem of the bioavailability of this

drug. As failure in dissolution rate of tested samples stand for more than 90% of failures, this indicates that, transport and storage conditions throughout Sudan may affect the quality of tested products .however as problem of substandard product found in Khartoum was at a level almost similar to other states (Figure 5). It's very difficult to suggest that transport conditions have significant contribution to the problem of substandard.

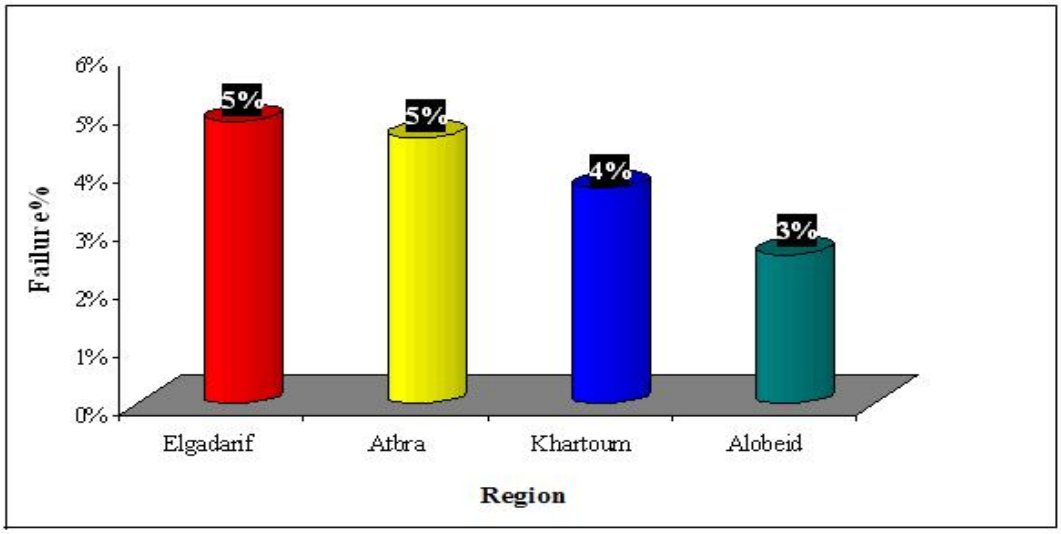
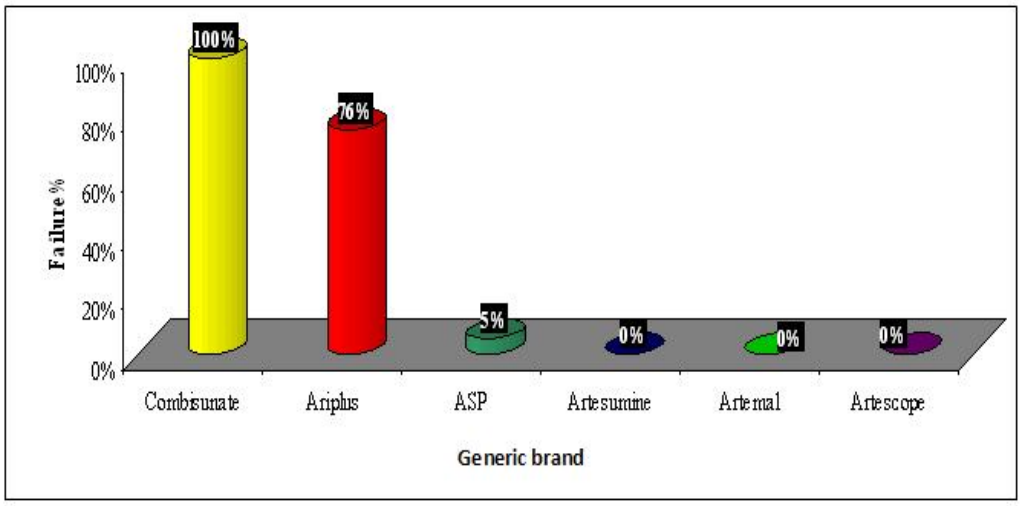


Figure No. (5): Percentage failures of artesunate tablets in different regions during the post- marketing surveillance



FigureNo. (6): Percentage failures of artesunate tablets according to generic brands

Figure (6) shows the results of percentage failure of the artesunate tablet according to their generic brands. The highest percentage failure was observed in Combisunate tablet, (100%) due to failure in the content, dissolution test and physical appearance followed by the Ariplus tablets (76%) due to dissolution test. ASP tablet (5%) failure in dissolution test, there was no failure in other generic brands (Artesumine, Artemal ,Artecosp tablets) . This confirms that the difference in the drug formulation may affect dissolution rate. However the rate of dissolution affected by several factors such as, the factors that relating to the solid Dosage Form (formulation factors, Processing factors and Compression Force), and that relating to the physicochemical properties of the drug (Effect of particle Size, Effect of the crystalline state of the Drug) (Remington, 2005).

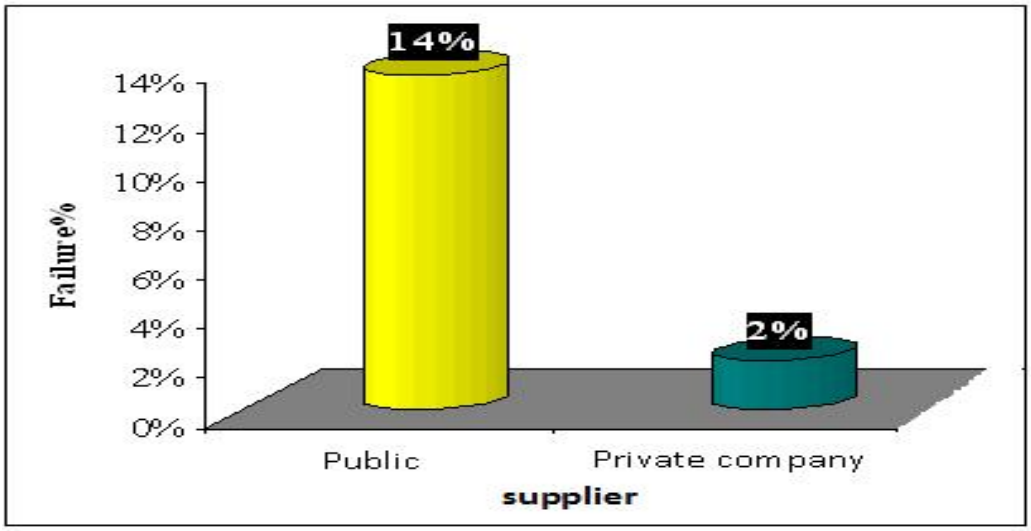


Figure No. (7): Percentage failure of artesunste tablets according to The Supplier

Figure (7) showed the results according to supplier (public or private), was expressed as percentage failure. The results showed a higher failure level in the public sector (14%) than the private supply system (2%). Failure level in the public was significant. As every government allocates substantial

portion of its total health budget to drugs (WHO, 1997), the current findings should raise an alarm to the authorities, It is important that the government should assure the quality of imported drugs.

4.2. Results of stability study of Artesumine tablets for adults and children stored at room temperature in different states of Sudan.

Three batches of Artesumine tablets for adult (100mg artesunate) and Three batches for children (50mg artesunate) were stored on shelves at room temperature in different regions of Sudan (Elobied ,Port Sudan, Atbara, and Khartoum) to represent West ,East, North, Center of Sudan. These also represent different climatic conditions in Sudan. The samples were tested at zero time, after 3, 6, 12, 18, 24 and 36 months (WHO, 2004).The samples were tested for the content of the active ingredient, dissolution, degradation product and physical appearance according to IP,2005 and Chinese pharmacopeia 1996.

Tables (9-16) show the combined results of results of stability study of Artesumine tablets (adults and children) stored at room temperature in different states of Sudan.The results showed that the percentage contents, dissolution rate and related substances of artesunate tablets were within the International Pharmacopeia limits. The results indicated that artesunate tablets are reasonably stable.The results also showed the presence of some degradation products. The detection of the degradation products varies according to the area where the artesunate tablets were stored. They were detected after 3 months in Khartoum and Port Sudan, 9 months in Elobeid and 24 months in Atbara. It is reported that artesunate tablets are affected by humidity (WHO, 2003). This difference in the detection time of the

degradation products may be due to the higher humidity and temperature in Khartoum and Port Sudan compared to Elobeid (tables 50-53 show the mean temperature and relative humidity in the areas of the study). Atbara is the least humid area and this may explain the late detection of the degredant. The results indicated that the stability of artesunate tablets is affected by temperature and humidity, but the effect of humidity is more than the temperature (WHO, 2003). The south of Sudan has a tropical climate (high humidity). Unfortunately not included in this study.

4.2.1. Kinetic studies on Artesumine tablets

The stability data of artesumine tablets for children Table (9) Batch. No. LS061601 and artesumine tablets for adults Batch. No. LS060602 in each state were analyzed to predict the effect of temperature on the rate of the reaction, order of Reaction, shelf life and half life.

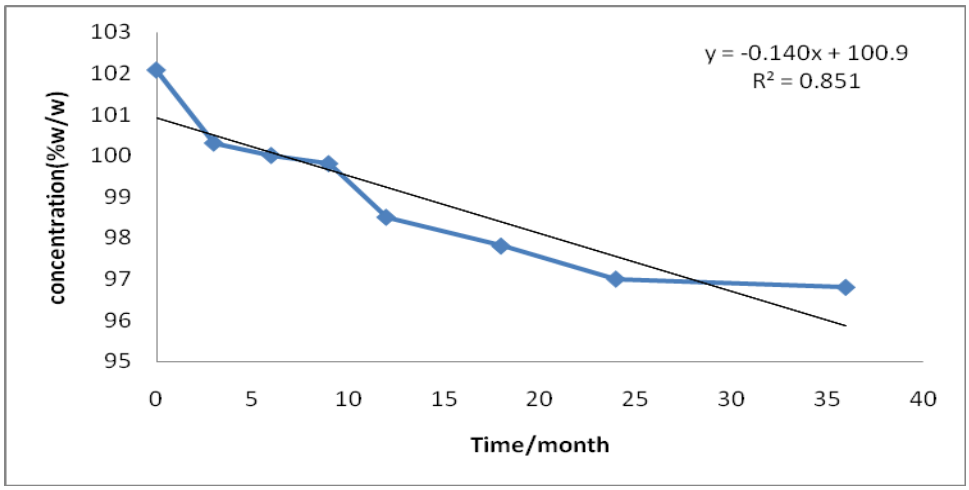


Figure No. (8): Zero order reaction kinetics of Artesumine tablets for adultsstore in Khartoum:

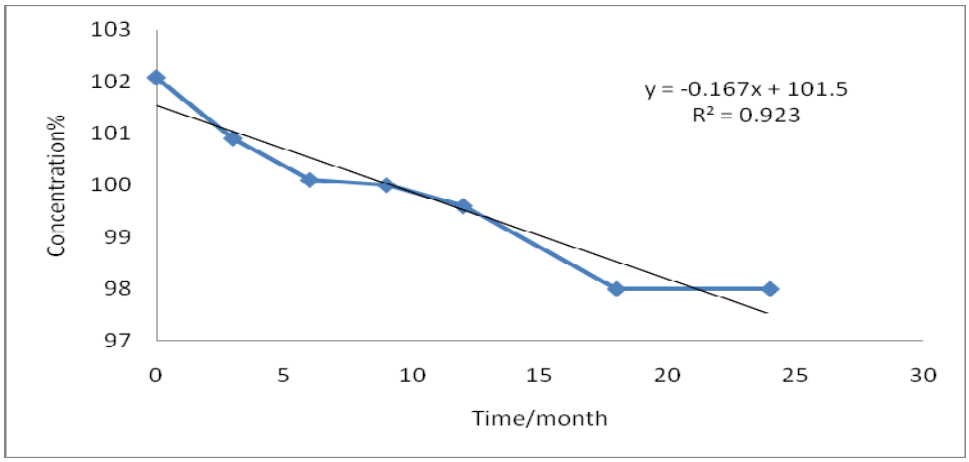


Figure No. (9): Zero order reaction kinetics of Artesumine tablets for adults store in Atbara:

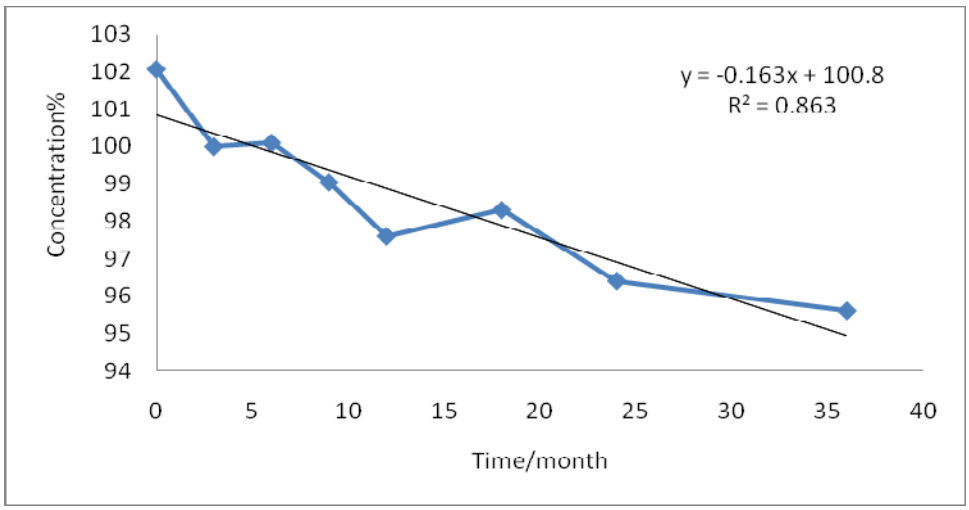


Figure No. (10): Zero order reaction kinetics of Artesumine tablets for adults store in Port Sudan:

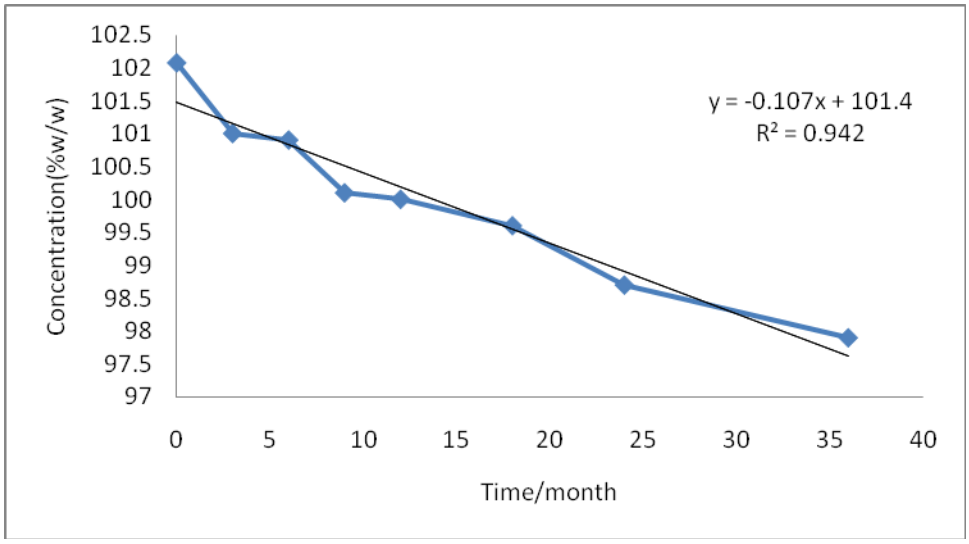


Figure No. (11): Zero order reaction kinetics of Artesumine tablets for adults store in Elobied:

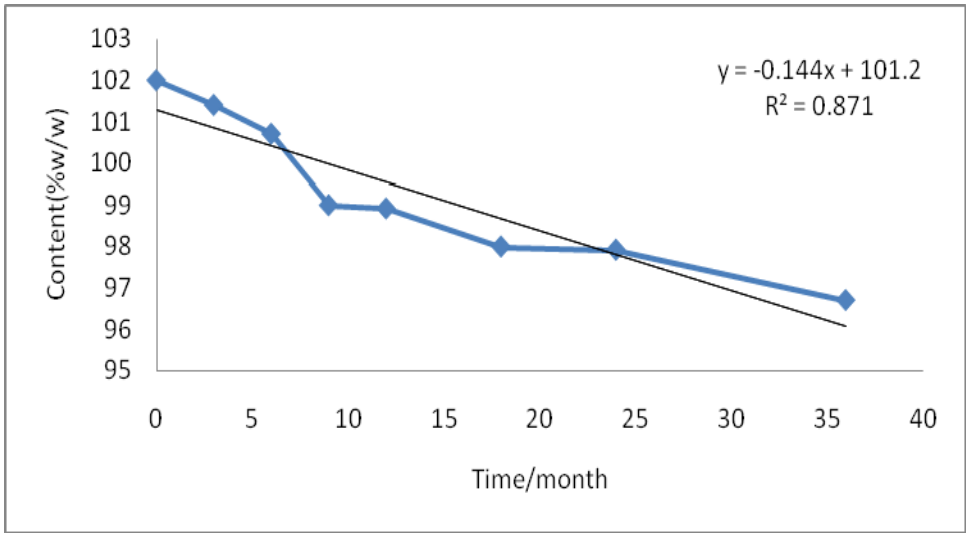


Figure No. (12): Zero order reaction kinetics of Artesumine tablets for children store in Khartoum:

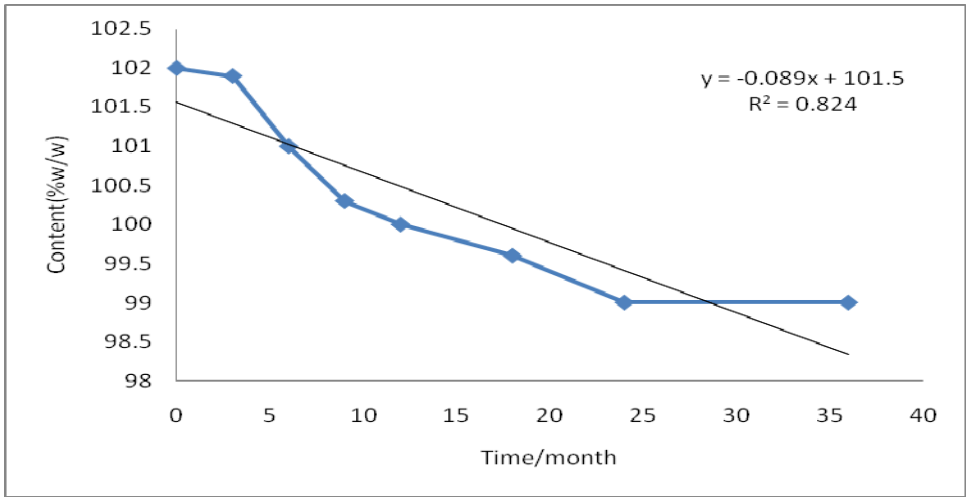


Figure No. (13): Zero order reaction kinetics of Artesumine tablets for children store in Atbara:

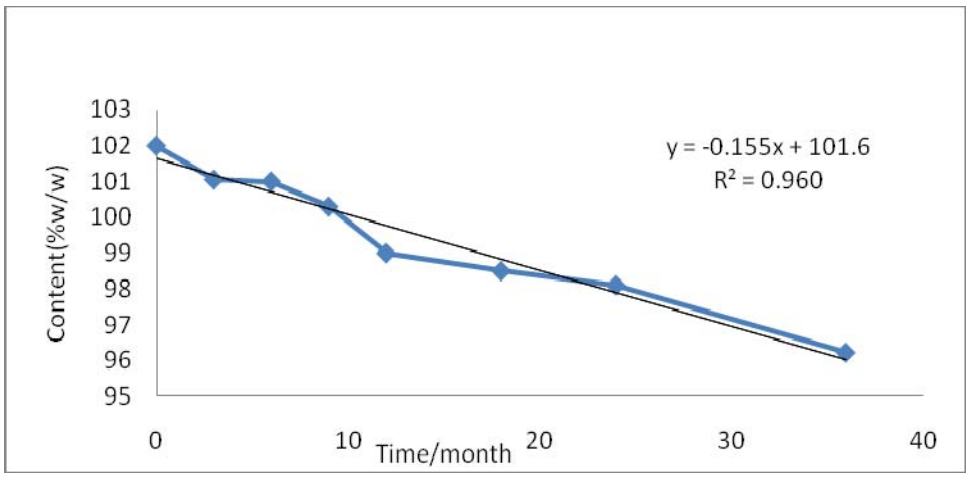


Figure No. (14): Zero order reaction kinetics of Artesumine tablets for childrenstore in Port Sudan:

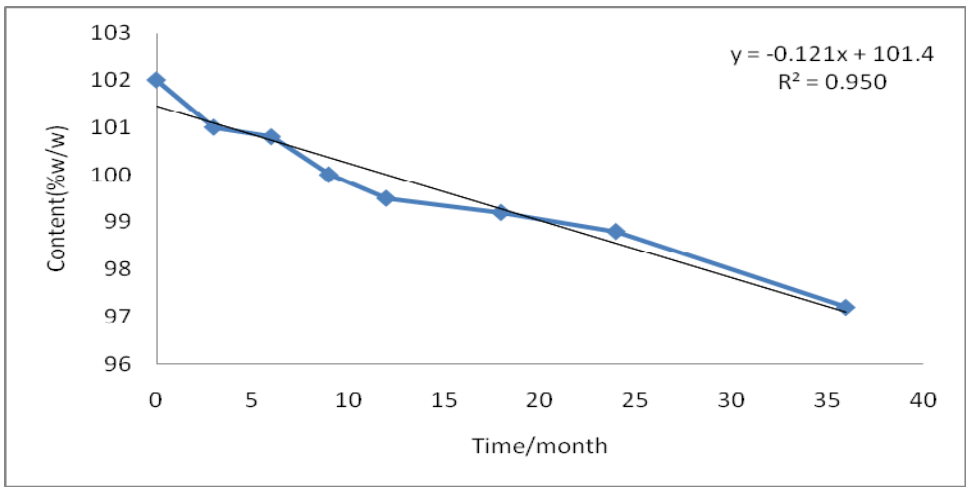


Figure No. (15): Zero order reaction kinetics of Artesumine tablets for children store in Elobied:

Figures (8-15) show that the results of reaction kinetics do not fit into any simple model of reaction kinetics .Many pharmaceutical processes, including certain degradation reactions ,do not fit into any simple model of reaction kinetics(Codex,1994). The best result for reaction kinetics of

Artesumine tablets for adults was obtained in Figure (11) and for children was obtained in Figure (14). The stability revealed zero order reaction kinetics.

In Figure (11) the calculated rate of reaction, t_{10} and t_{50} were:

K= -slop

t_{10} = 0.1a/K

t_{50} = 0.5a/K

K =-0.107

t_{10} =0.1x101.4/ 0.107= 94.7 months

t_{50} =0.5 x101.4/0.107 = 473.8months

In Figure (14) the calculated rate of reaction, t_{10} and t_{50} were:

K =-0.155

t_{10} =0.1x102.0/ 0.155= 65.8 months

t_{50} =0.5 x102.0/0.155 = 329.0months

Although it is often convenient to express shelf-life solely in terms of the chemical stability of the active constituent, it is essential that the other desirable properties of the product are retained during storage. Physical may on storage lead to a decrease in dissolution rate and bioavailability and thus decrease in efficacy (Codex, 1994).The results obtained showed that the stability of artesunate was affected by the decrease in dissolution test .It is difficult to predict it's shelf life exactly by doing a real time test at ambient

temperature. Furthermore the variation in the temperature during the years throughout the study makes the prediction of the shelf life difficult because the study of the reaction kinetics needs constant temperature (Codex, 1994). The real time tests at ambient conditions are the only true indication of shelf life (Codex, 1994).

4.3. Results of comparison of different brands of artesunate tablets (AS+SP) stored at room temperature in NDQCL

Five brands of (AS+SP) tablets for adult(100mg artesunate)and for children(50mg artesunate) from Central Medical Supply (CMS) stores and private companies were stored in the National Drug Quality Control Laboratory NDQCL on shelves at room temperature and tested at zero time, after 3, 6, 12, 18, 24 and 36 months(WHO,2007). The study was developed to detect the quality of these brands at the same storage condition. The samples were tested for the content of the active ingredient, dissolution, degradation product and physical appearance 0f artesunate tablets according to IP,2005 and Chinese pharmacopeia,1996.

Tables (17-26) show the combined results of different generic brands of artesunate tablets stored in NDQCL at room temperature. The results showed failure in the dissolution test for all Ariplus tablets. ASP tablets, which are locally made, reached the lower limit of the pharmacopoeia standards for dissolution test at the end of the shelf life (24months). When the results in tables (17-26) were compared with the results in Tables (1-8) for post- marketing surveillance, the comparison indicated that the same batches of Ariplus tablets that failed the dissolution test in the NDQCL failed the dissolution test in all states. This means that the failure may be due to the storage conditions rather than the transportation. The results in tables

(17-26) showed no failure in the percentage content for all generic brands. Although there is one degradation product detected in all generic brands after three months, the test of related substances remained within the Pharmacopeia limit<0.1% (less than the detectable limit of the IP pharmacopeia 2005). The Artesumine and Artecosp tablets from Guilin Company showed the best results of dissolution rate and percentage content. This is clearly due to the high quality of Artecosp and Artesumine tablets which are the only products prequalified by WHO (WHO, 2007). The difference in the dissolution rate between different brands may be due to the difference in the drug formulation that affects the rate of the dissolution of the tablets (Remington 2005). Also the difference of the dissolution rate indicates problem of bioavailability of this drug .Hence the bioequivalence study is needed in the registration of the artesunate tablets. This study indicates that not all artesunate tablets present in Sudanese market conform to the standards of quality.

4.4. Results of detection of of artesunate degredant by HPLC method

Different batches of Artesumine tablets (artesunate 50mg and 100mg) stored in different regions of Sudan, and different generic brands of artesunate (AS+SP) stored in (NDQCL) at room temperature were analyzed directly after clearance from the supplier(at zero time. Figure (16) shows the HPLC chromatogram of Artesumine tablet for adult at zero time.

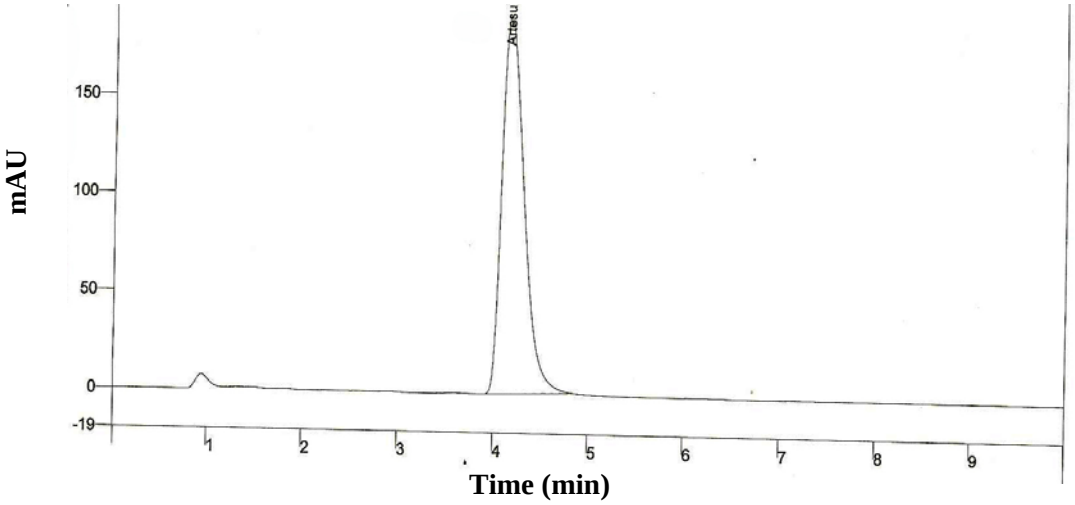


Figure No. (16): HPLC chromatogram of Artesumine tablets at zer time

An HPLC chromatogram of artesunate at zero times in figure (16) shows acetonitrile peak at 0.9min.and peak of the artesunate at retention time of 4.1min.

The results of different batches of Artesumine tablets (50mg and 100mg artesunate) in the post-marketing surveillance, and that stored at room temperature for three months showed degradation product of artesunate (Figure 17).

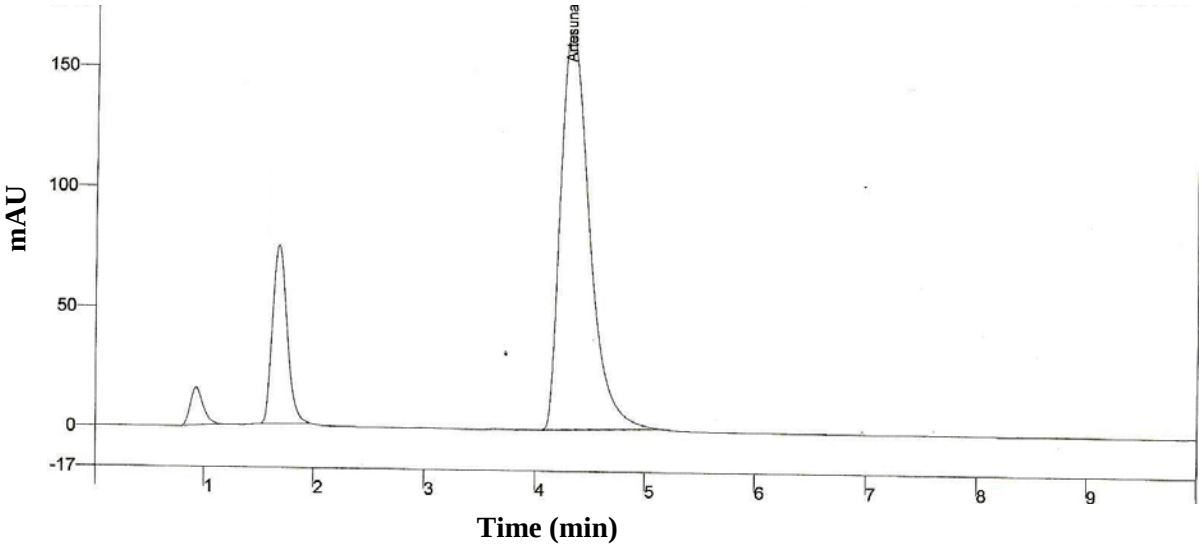


Figure No. (17): HPLC chromatogram of Artesumine degradant

In figure (17) three peaks were detected at different retention times, acetonitrile peak at 0.9min., degradant peak at 1.6 min. and the main artesunate peak at 4.3 min. To know the type of the degradant of the artesunate tablets in this study, a new published method for assay and detection of impurities of Artesunate tablets (Ema, 2009 method) was used. IP (2009) also published a draft method which is the same as Ema(2009) method for assay and detection of impurities of Artesunate tablets. IP(2009) draft reported four peaks of artesunate and it's impurities, these are, α-dihydro-artemisinin(α -DHA) at retention time 5.0 min., β-DHA at retention time 8.0 min., artemisinin at retention time 11.5min and the main peak of artesunate at retention time 9 min. This new method was employed because it gave good resolution of peaks for the expected degradants of the artesunate namely dihydroartemisinin(DHA). The old assay method of the artesunate tablets (IP,2005) did not give good resolution of peaks for the expected degradants DHA as shown in the HPLC chromatogram of DHA Figure (18).

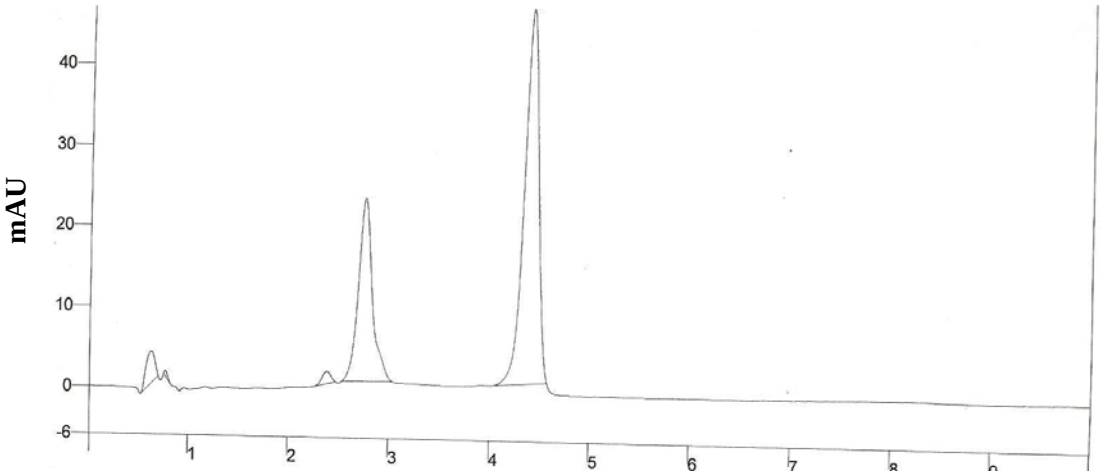


Figure No. (18): HPLC chromatogram of dihdroartemisinin powder using IP(2005) method

The HPLC chromatogram of dihdroartemisinin pure powder in figure (18) shows main peak of DHA at retention time 4.3min. which is the same as the retention time of the main peak of artesunate in Figure(17) when used the old method(IP2005).For this reason the published method IP(2009) was used instead of IP(2005) method for detection of the artesunate degradants.

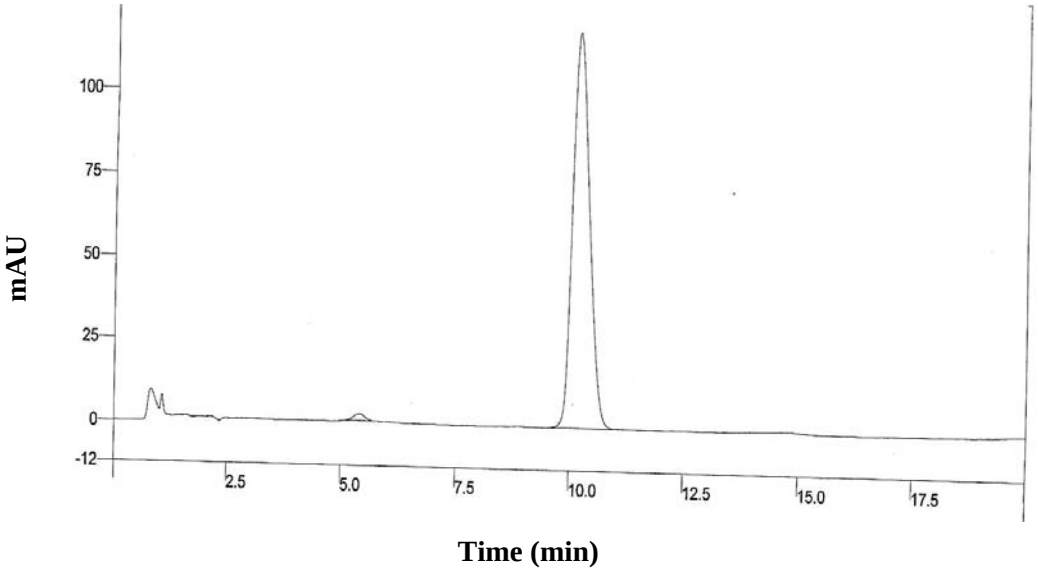


Figure No. (19): HPLC chromatogram of Artesumine tablets using (IP,2009) method

An HPLC chromatogram of Artesumine tablets (100mg artesunate) using IP (2009) method, Figure (19), shows two peaks(degradant peak at retention time of 5.4min., and the main peak of artesunate at retention time of 10.1 min).

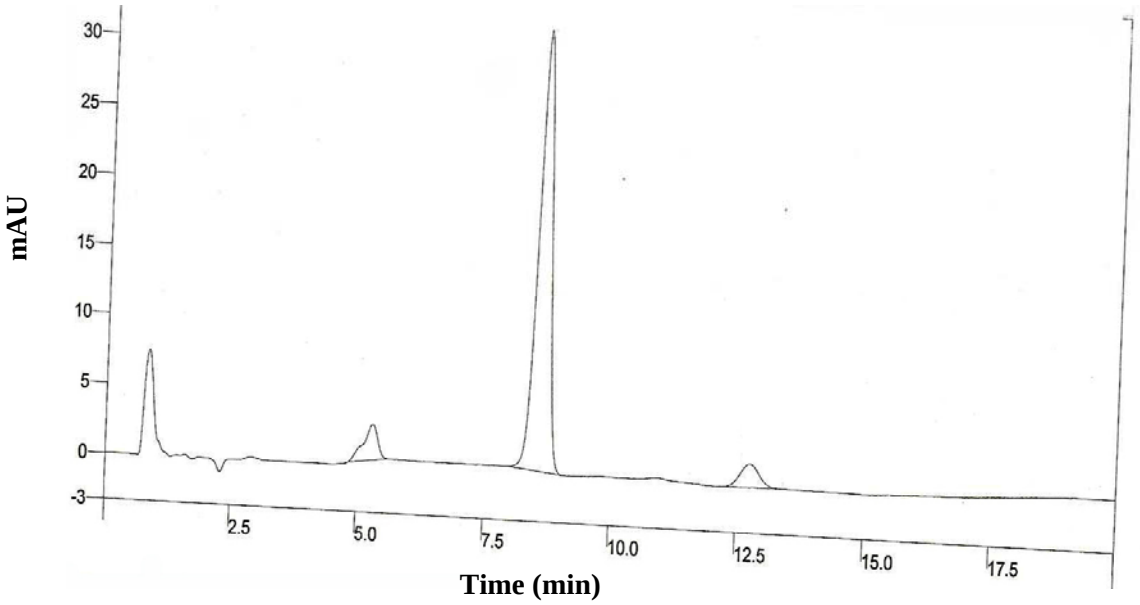


Figure No. (20): HPLC Chromatogram of dihydroartemisinin pure powder using (IP, 2009) method

An HPLC Chromatogram of dihydroartemisinin pure powder using IP(2009) method in figure (20) shows three peaks(peak at 5.3min., main peak of dihydroartemisinin at 8.5mn and peak at 12.7min). The results obtained in Figure (19) showed degradant of artesunate at retention time (5.4mn) and Figure (20) showed degradant of dihydroartemisinin (DHA) at the same retention time of 5.4min.

Comparing the retention times of the artesunate degradant (Figure 19) with the retention time of the impurities peaks that reported by the IP(2009) the results indicated that the degradant obtained is α-DHA which appears at retention time 5.0 min. in the IP(2009).

For further confirmation of the type of degradant of the Artesumine tablets, three solutions were prepared. Solution (1) was from Artesumine tablets consisting of a quantity equivalent to 0.05g/ml artesunate in acetonitril. Solution (2) consists of 0.1g/ml 0f dihydroatemisinin pure powder in acetonitrile. Solution (3) consists of a mixture of Artesumine tablets (equivalent to 0.05g/ml artessunate) and 0.1g/ml dihydroatemisinin pure powder, in acetonitrile. Each solution was subjected to analysis by HPLC. The chromatograms of solution (1),(2), and (3) are shown in Figures (21), (22) and (23) respectively.

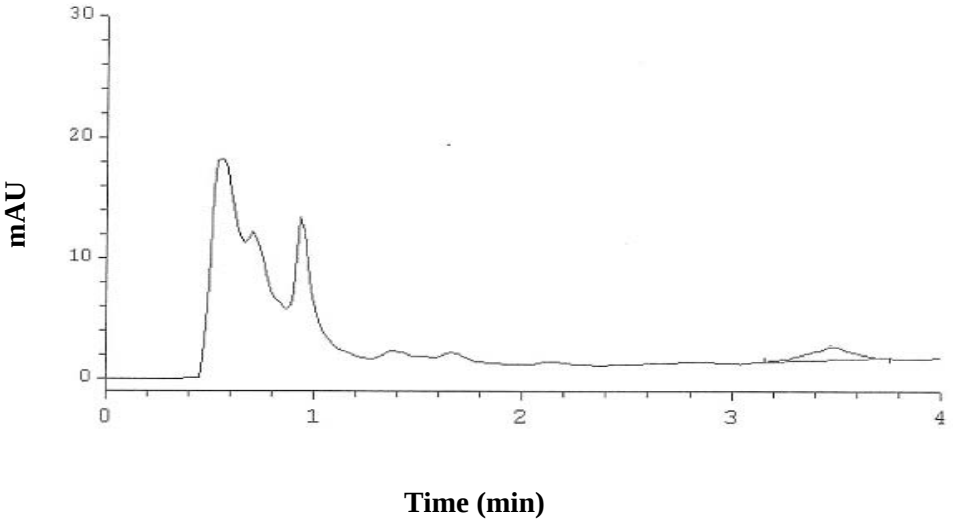


Figure No. (21): HPLC Chromatogram of artesunate degradant

The HPLC chromatogram of the artesunate degredant in figure (21) shows a peak at retention time 3.5 min.

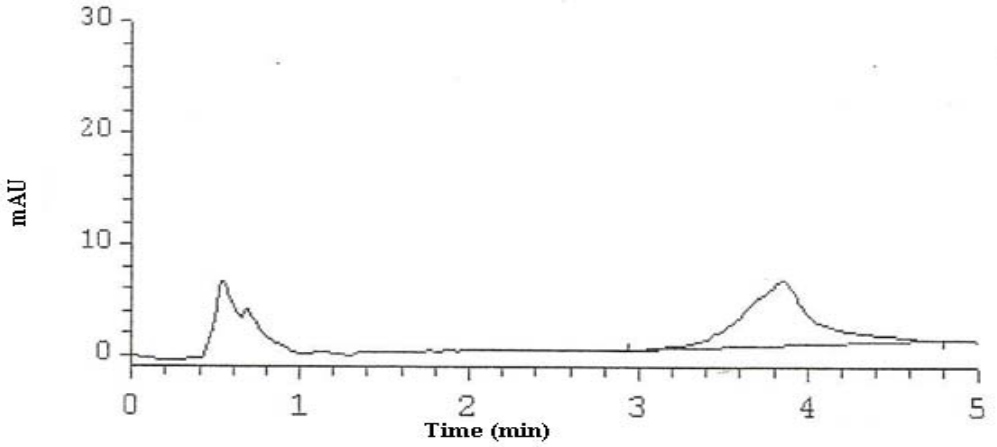


Figure No. (22): HPLC Chromatogram of dihydroartemisinin degradant

The HPLC chromatogram of dihydroartemisinin degredant in Figure (22) shows a peak at retention time 3.8min.

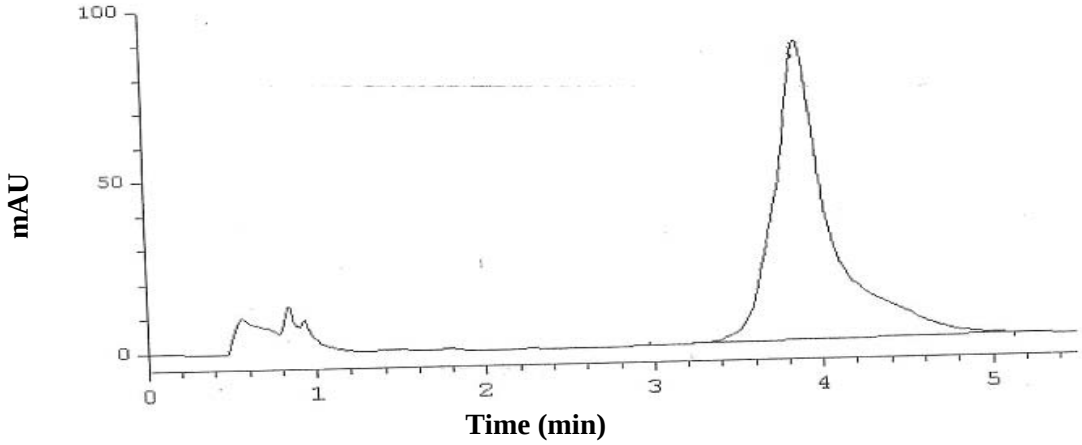


Figure No. (23): HPLC chromatogram of the combined solutions of artesunate 100mg tablets and DHA powder

The HPLC chromatogram of the combined solutions of Artesumine tablets and dihydroartemisinin pure powder (Figure 23) shows one peak at retention time of 3.9min. with increased area under the peak of the degredant. The results obtained confirmed that the artesunate degredant is one of the dihydroartemisin degredants namely (α-DHA).

4.5. Results of the adopted dissolution test method.

New method of dissolution test was adopted. Validation of the method was carried out according to the validation protocol of the USP(2007) and WHO guidelines (2007). Validation parameters. Four batches of artesunate tablets (three batches 100mg and one batch 50mg artesunate) were used. .Samples were analyzed in two laboratories (NDQCL and NCL Khartoum). Six tablets of artesunate were introduced into the dissolution vessels contains 900ml of dissolution media. The system set at 37C° using apparatus 2(paddle), the rotational speed of the paddle was 100 rpm. A quantity of the dissolution media in the different vessels were withdrawn after 45 minutes, and filtered with membrane filter having porosity of 0.45µ and without any further dilution, the samples were analyzed for artesunate content by HPLC method,using mixture of 44 volume acetonitrile and 56 volume phosphate buffer pH3.0.The separation was carried out using C18 columnwith flow rate 1.3 ml/min,at wave length 216 nm. The Results were compared with the dissolution method of the Chinese Pharmacopeia (1996).

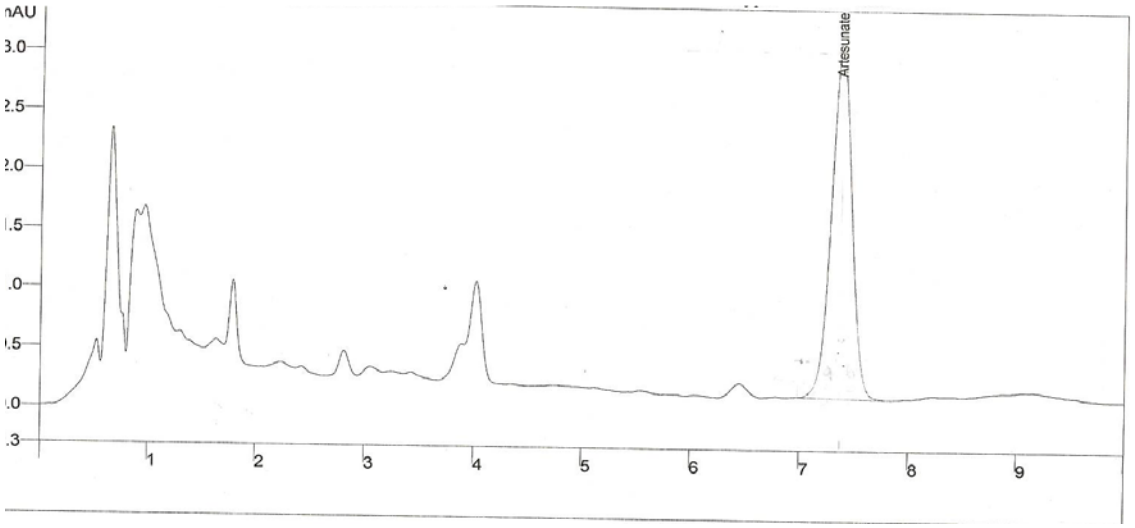


Figure No. (24): HPLC chromatogram of Artesumine tablets (for adults) using the proposed dissolution test method

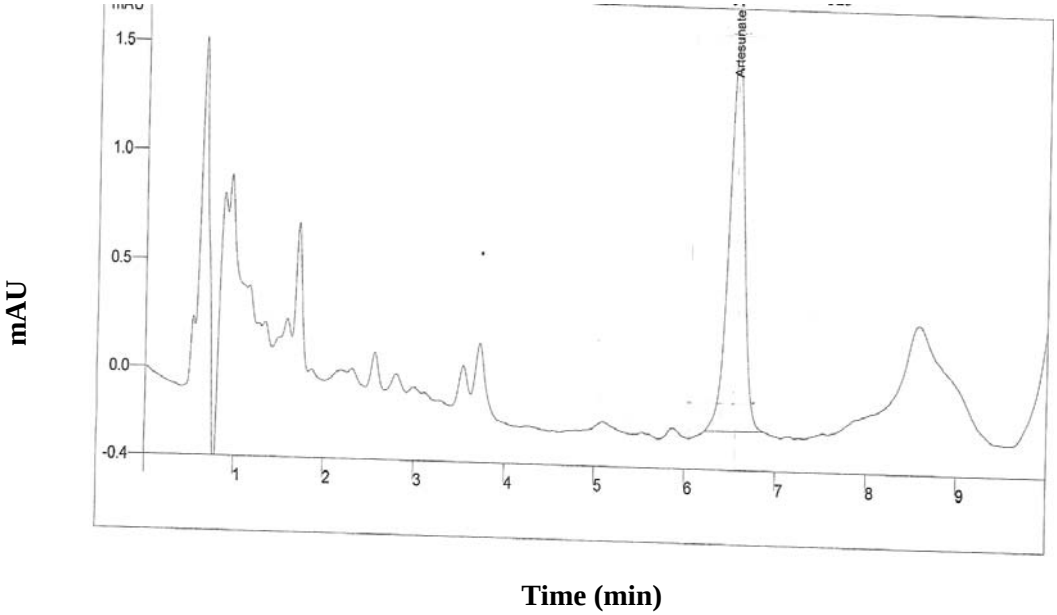


Figure No. (25): HPLC chromatogram of Artesumine tablets (for children) using the proposed dissolution test method

Figures (24&25) show HPLC chromatograms of the dissolution test of the Artesumine tablets for adults and children respectively using proposed

method.The chromatograms in Figure (24) showed a peak of artesunate with peak asymmetry (b/a) 0.3/0.3 = 1. And Figure (25) showed a peak of artesunate with peak asymmetry (b/a) 0.3/0.4 = 0.75.

4.5.1. Validation of the adopteded dissolution method.

4.5.1.1. Specificity

Specificity was examined by analyzing a solution of the expected degradants (Figure26), and a solution of a mixture of the expected degradants (artemisinin and dihydroartemisinin) and artesunate pure powder (Figure27).The chromatograms show peaks at retention time at 4.2 min. for dihydroartemisinin , at 7.0 min. for artesunate and at 9.3 min.for artemisinin. No interference was observed.

Different dosage forms (Artemal, ASP, and Artesumine tablets) were analyzed using the UV- spectrophotometric method (Reference method)and HPLC method(Proposed method) to investigate the interference of the exciepients with the active ingredient of artesunate .The results are compared as presented in tables(27-29).The results obtained by the Proposed method showed that there was no exciepients interference in the formulations analyzed.

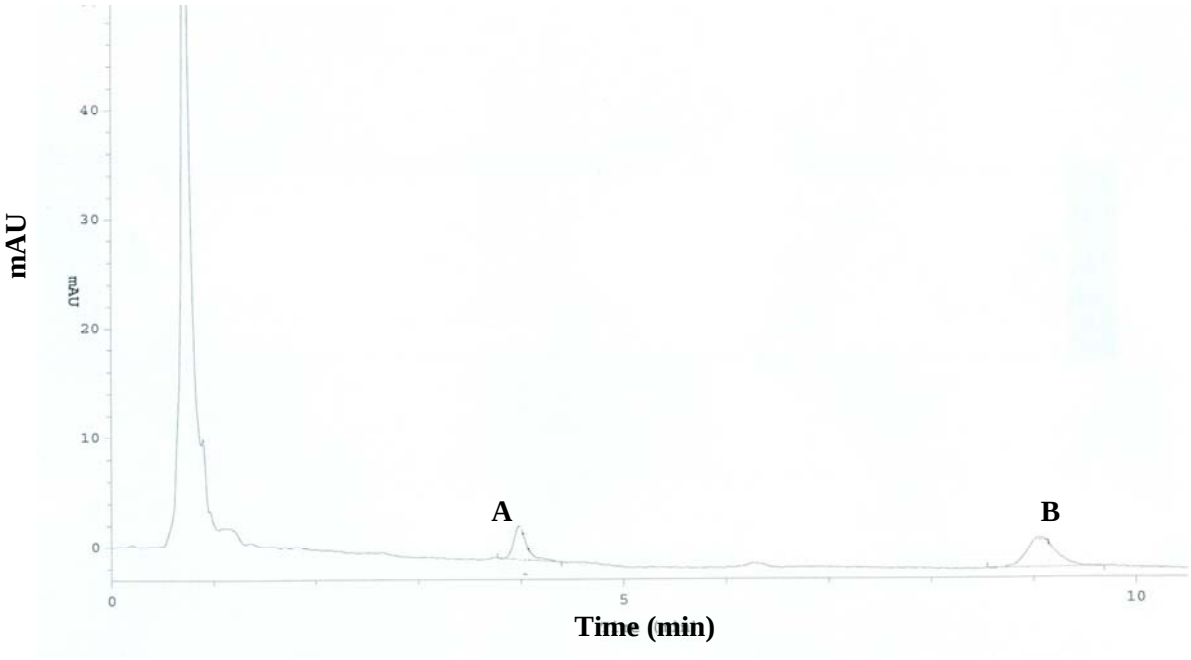


Figure 26: Aypical HPLC chromatorram of artesunate degredants(artemisinin (B) and dihydroartemisinin (A)).

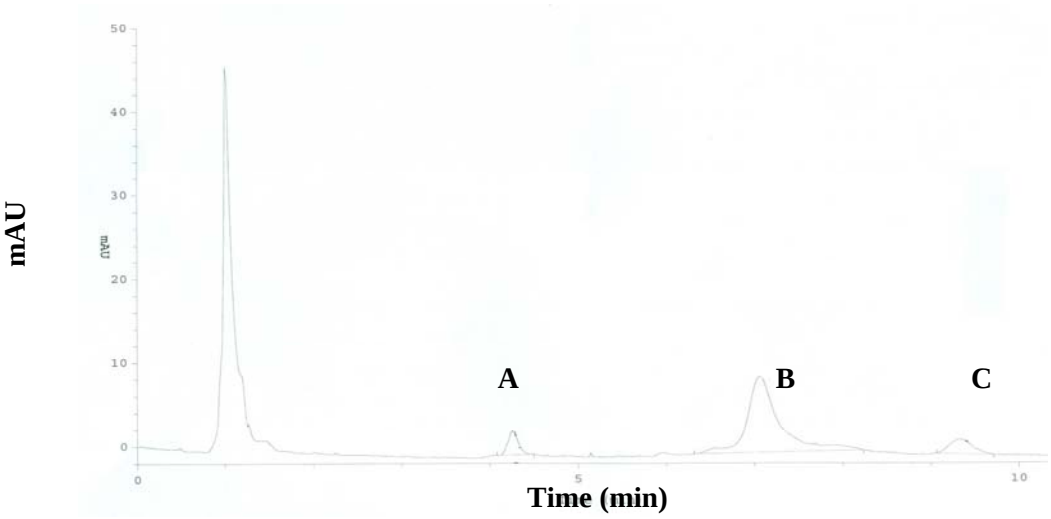


Figure 27: Typical HPLC chromatorram of artesunate (B) and it's degredants(artemisinin (C) and dihydroartemisinin (A)).

Table No.(27): Results of specificity of the adopted dissolution test method(Artemal tablets for children) Batch No. 08051.

sample	Reference method %released	Proposed method %released
1	89.04	91.94
2	87.15	89.09
3	96.66	92.96
4	94.08	93.52
5	94.55	89.28
6	81.91	95.80
Mean:	90.7	92.09
N	6	6
% RSD:	5.86	2.57
ST.Error Mean	2.17	0.96

Calculated t-value=0.605

Tabulated t-value=2.23(at 95%cofidence level)

Table No. (28): Results of specificity of the adopted dissolution test method(ASP tablets for children) Batch No. 091002.

sample	Reference method %released	Proposed method %released
1	83.04	81.07
2	86.36	84.3
3	85.04	79.61
4	83.72	81.07
5	81.88	78.13
6	79.51	82.00
Mean:	83.25	81.03
N	6	6
% RSD:	2.89	2.59
ST.Error Mean	0.98	0.86

Calculated t-value=0.094

Tabulated t-value=2.23(at 95%cofidence level)

Table No. (29): Results of specificity of the adopted dissolution test method (Artesumine tablets for children) Batch No. LS060601.

sample	Reference method %released	Proposed method %released
1	90.1	91.85
2	88.3	90.64
3	86.87	89.78
4	90.61	89.22
5	88.89	91.3
6	89.11	92.36
Mean:	**88.98**	**90.85**
N	6	6
% RSD:	1.49	1.33
ST.Error Mean	**0.54**	**0.49**

Calculated t-value=2.54

Tabulated t-value=2.23(at 95%cofidence level)

4.5.1.2. Linearity

The linearity of the adopted method for dissolution test of artesunate tablets response was evaluated from 40-120µg/ml range. Concentration (40-120µg/ml) versus area under the peak, Figure (26) showed correlation coefficient of 0.999.

Table (30): Calibration data of artesunate using the adopted HPLC method for dissolution test

Concentration in µg/ml	Peak area of atresunate pure powder
40	84569
50	105712
60	125854
70	147999
80	175149
90	190382
100	211424
110	232567
120	253709

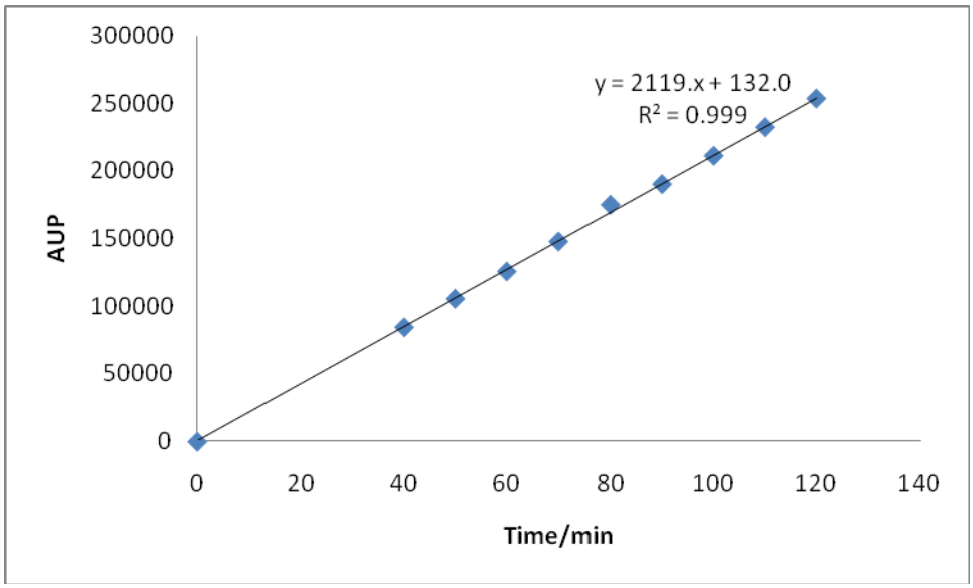


Figure (28): Calibration curve of artesunate using the adopted HPLC method for dissolution test.

4.5.1.3. Accuracy

The accuracy of the adopted HPLC method (method 2) was evaluated, tables (31-34). Four batches were subjected to dissolution test conditions and analyzed by method 2. The results were compared with those obtained by the UV-spectrophotometric method (Chinese Pharmacopeia ,1996) (method 1), and calculated as the difference between the mean and the acceptance true value at 95% confidence level ,with degree of freedom equal 10[n-1(12-2=10)] .It was found that the standard error of the mean for all batches was less than the standard error of the means obtained by the UV-spectrophotometric method(Miller and Miller,2005).The results obtained by the adopted HPLC method showed no significant difference from those obtained by the official U.V method. The calculated t-values for samples by the HPLC method in different laboratories were 0.14, 2.17, 0.12, and 0.84, which were less than the tabulated ones 2.23. This indicates that the adopted method is accurate (Miller and Miller, 2005).

Table No. (31): Determination of accuracy of the adopted dissolution test method (Artesumine tablets for adults batch.no.LS060301)

sample	Refrence method %released	Proposed method %released
1	89.79	91.94
2	87.15	89.09
3	96.66	92.96
4	94.08	93.52
5	94.55	89.28
6	91.91	95.80
Mean:	92.36	92.09
N	6	6
Sd	3.26	2.58
% RSD:	3.76	2.80
ST.Error Mean	1.41	1.05

Calculated t-value=0.14

Tabulated t-value=2.23(at 95%cofidence level)

Table No. (32): Determination of accuracy of the adopted dissolution test method (Artesumine tablets for adults batch.no.LS060602)

sample	Refrence method %released	Proposed method %released
1	101.7	89.54
2	92.0	86.61
3	89.0	89.4
4	91.1	87.9
5	90.0	89.03
6	91.0	86.46
Mean:	92.46	88.16
N	6	6
Sd	4.65	1.38
% RSD:	5.02	1.56
ST.Error Mean	1.89	0.56

Calculated t-value=2.17

Tabulated t-value=2.23(at 95%cofidence level)

Table No. (33): Determination of accuracy of the adopted dissolution test method (Artesumine tablets for adults batch.no.LS060401)

sample	Refrence method %released	Proposed method %released
1	92.66	92.52
2	94.12	94.34
3	97.5	94.39
4	91.21	92.96
5	95.72	93.76
6	93.69	96.17
Mean:	94.15	94.02
N	6	6
Sd	2.22	1.21
% RSD:	2.36	1.37
ST.Error Mean	0.91	0.52

Calculated t-value=0.12

Tabulated t-value=2.23(at 95%cofidence level)

Table No. (34): Determination of accuracy of the adopted dissolution test method (Artesumine tablets for children batch.no.LS060401)

sample	Refrence method %released	Proposed method %released
1	83.12	85.79
2	84.36	84.19
3	81.37	83.69
4	85.85	82.99
5	81.11	81.19
6	81.11	84.26
Mean:	82.82	83.68
N	6	6
Sd	1.98	1.53
% RSD:	2.39	1.83
ST.Error Mean	0.81	0.62

Calculated t-value=0.84

Tabulated t-value=2.23(at 95%cofidence level)

4.5.1.4. Precision (reproducibility)

The precision of the method was determined by measuring the reproducibility in two laboratories, tables (35-38) .The percentage relative standard deviations are within the acceptance criteria of 5% (USP, 2007). The calculated F-values for samples by the adopted method were 1.88, 3.7, 1.63, which were less than the tabulated ones 5.05. This confirms that the adopted method is reproducible.

TableNo.(35)Determination of reproducibility of the adopted dissolution test method (Artesumine tablets for adults batch.no.LS060602)

sample	Laboratory(1) %released	Laboratory(2) %released
1	97.40	89.54
2	91.45	86.61
3	91.24	89.4
4	90.56	87.9
5	87.76	89.03
6	88.08	86.46
Mean:	91.08	88.15
N	6	6
Sd	3.47	1.38
% RSD:	3.34	1.57

Calculated F-value=3.7

Tabulated F-value=5.05(at 95%cofidence level)

TableNo.(36):Determination of reproducibility of the adopted dissolution test method (Artesumine tablets for adults batch.no.LS060401)

sample	Laboratory(1) %released	Laboratory(2) %released
1	97.0	92.52
2	96.1	94.34
3	96.29	94.39
4	96.0	92.96
5	98.02	93.76
6	98.07	96.17
Mean:	96.9	94.02
N	6	6
Sd	0.94	1.28
% RSD:	0.97	1.37

Calculated F-value=1.88

Tabulated F-value=5.05(at 95%cofidence level)

TableNo.(37):Determination of reproducibility of theadopted dissolution test method (Artesumine tablets for children batch.no.LS060401)

sample	Laboratory(1) %released	Laboratory(2) %released
1	85.16	85.79
2	85.79	84.19
3	84.85	83.69
4	83.91	82.99
5	83.83	81.19
6	82.42	84.26
Mean:	84.32	83.68
N	6	6
Sd	1.19	1.53
% RSD:	1.42	1.82

Calculated F-value=1.63

Tabulated F-value=5.05(at 95%cofidence level)

4.5.2. The advantages of the adopted dissolution test method on other Pharmacopeial methods:

1. In the adopted dissolution method, samples are analyzed by HPLC method which is more selective than UV-spectrophotometric method (Chinese Pharmacopeia, 1996). Also the assay of the samples is performed directly after filtration. While in the Chinese pharmacopeia method (1996) several steps are needed to detect the samples after filtration.

2. The adopted method is off-line filtration techniques for filtration of dissolved samples. While the IP 2009 method needs in-line filtration techniques which is not affordable by most developing countries. Moreover the samples under test need to be detected without delay, which means that the results affect by time. This is not the case in the adopted method. Also IP method needs injection volume of 100 µl to detect the samples, while the adopted method needs 20µl to give response for 50mg and 100mg artesunate. Because, artesunate is

practically insoluble at all pH and sparingly soluble in water (Indian pharmacopeia,2009), thus in the adopted method 0.2% Na lauryl sulphate was added to dissolution medium to increase the solubility of the artesunate . In case of IP method only buffer 6.8 is used.

3. The adopted method is not expensive compared to the Indian Pharmacopeia method 2009 (HPLC method) for analysis of samples which needs special device to adjust the column temperature at 15°C.While in the adopted HPLC method the analysis carried out at room temperature (30°C) . Moreover, in the Indian Pharmacopeia method 50µ is needed to detect the samples by HPLC, because the dissolution medium used is phosphate buffer pH5.0.

Chapter 5
Conclusion & Recommendations

5.1. Conclusion

- Substandard products exist within the drug distribution chains in Sudan. In view of the potential danger that substandard antimalarials could already be pose and in the fight against malaria, an intervention plan should be developed immediately. This could involve setting up quality surveillance systems within drug regulatory authorities in Sudan. There is a need for more carefully planned studies in order to define quality problems further.
- Although the humidity and temperature in all states of Sudan affected the artesunate molecule causing a degradation product which is one of the dihydroartemisinin degredant namely (α-DHA), the results showed reasonable stability of artesunate .There are areas of high humidity in south of Sudan (tropic condition) not involved in this study, because of the situation. Thus there is a need for further study in these areas.
- Analysis of different generic brands of artesunate tablets showed that there is a significant problem of the drug formulation .Failure in dissolution test of one generic brand after three months storage at room temperature and other generic brand reach the lower limit of the dissolution test is a problem of low quality drugs registered in Sudan. The study indicates that not all artesunate generic brands present in Sudanese market conform to the standards of quality. Further investigation will be important especially for local manufacturers since it is easier to act and correct problem that involve domestic manufacturers. There is need for the regulatory authorities in Sudan to improve the quality of the of antimalarials drugs in Sudan and support manufacturers to improve GMP compliance.

- The development of cost-effective analytical protocol for artemisinin and its derivatives has become very important in the face of increasing supply and demand for this antimalarial agent. The adopted dissolution method for artesunate tablets can be employed in poorly equipped laboratories. The proposed method is selectiveive, precise and accurate.

5.2. Recommendations

- Appropriate storage conditions for artesunate tablet (AS+SP) must be ensured to maintain product stability and integrity.
- The product(s) should be appropriately blister-packed and stored in a cool place to assure maximal stability and product integrity.
- Artesunate tablets (AS+SP) should be procured from pharmaceutical companies with an assured competence to manufacture the product(s) according to GMP standards, and to concentrate on the prequalified manufacturers.
- Ministry of Health must ensure rational deployment of (AS+SP) with regimen adherence for optimal treatment and to prolong the useful therapeutic life of these drugs by comprehensive monitoring and evaluation of product use, through the post-marketing surveillance.
- Bioequivalence studies must be a principal issue for registration of drugs in Sudan.
- The adopted dissolution test method for artesunate tablet can be used in a routine test as it is selective, precise and accurate.

Chapter 6

References

1-Abu-Reid L.O.,EL-Samani S.A., Hag Omer A.I.,Khalil N.Y., Mahgoub K.M., Everittt G., Grundstrom K., Lindgren B., and Stjernstrom N.E.,1990. Stability of drugs in the tropics. A study in Sudan, J.Int. pharm., Vol.4:6-10.

2-Alfadl A.A., Abdoon S., Elamin M.,Garelnabi N., 2006. Quality of Antimalarial Drugs in Sudan: Results of Post-marketing Surveillance. Sudanese .J public health, Vol.1, 108-111

3-Amin A.A., Snow R.W., Kokwaro G.O., 2005. The quality of sulph-adoxine-pyrimethamine and amodiaquine products in the Kenyan retail sector. J Clin Pharm Ther; 30:559–565.

4-Agarwal S.P., Ali A., Shipra A., 2007. HPTLC determination of artes-unate as bulk drug and in pharmaceutical formulations. Indian J Pharm Sci .69:841-

5-Alin M.H., Björkman A, Landberg-Lindgren A., and Ashton M., 1992. The effect of artemisinine, its derivatives and mefloquine against chloroquine resistant strains of Plasmodium falciparum in vitro. Trans R Soc Trop Med Hyg 86:365-7.

6-Ambroise T. P., 1999. Current data on major novel antimalaria drugs: Artemisinin (qinghaosu) derivatives. Bull Acad Natl Med 183:797-80.

7- Gamil A., Eltabyeb K., Elniema E., 2008.The effect of environmental condition of Sudan on the stability of drug product. Personal communication

8-Benakis A., Paris M., Loutan L., Plessas C.T., Plessas S., 1998. Pharma-cokinetics of artemisinin and artesunate after oral administrationin in healthy volunteers. Am .J. Trop Med Hyg 56:17–23.

9-Bangchang K. Na., Congpuong K., Hung L., Molunto.N.P., and Karbwang J., 1998. Simple high-performance liquid chromatographic method with elec-trochemical detection for the simultaneous determination of artesunate and dihydroartemisinin in biological fluids, J Chroma Biomed Sci.24;708(1-2):201-7.

10-Basco L.K., 2004. Quality of antimalarial drugs used for self-medication. Am J Trop Med Hyg, 70:245-250.

11-Batty K .T., Ilett K. F., Davis T., Davis M. E., 1996. Chemical stability of artesunate injection and proposal for its administration by intravenous infusion. J pharm and pharmacology 48(1):22-6.

12-BP, 2005. Supplementary chapter. E.disssollution Testing of Solid Oral Dosage Form. page 757-267

13-Charles M., Clive O., 2003. The quality of antimalarials study in selected African countries.Essential Drugs and Medicines Policy.WHO-/EDM-/PAR/.4.

14-Caudron J..M., Ford N., Henkens M., Macé C., Kiddle M. R., Pinel J., 2008. Substandard medicines in resource-poor settings: a problem that can no longer be ignored. Trop Med Int. Health; 13:1062–1072.

15-Chawira A. N., Warhurst D. C., and Peters W., 1986. Qinghaosu resistance in rodent malaria. Trans R Soc Trop Med Hyg 80:477-480.

16-Cao, X.T., Betell D.B., PhamT.P.,TaT.T.,TranT.N.,NguyenT.,Pham T.T., Day N. P, and White N. J, 1997. Comparison of artemisinin suppositories, Intramuscular artesunate and intravenous quinine for the treatment of severe childhood malaria.Trans R Soc Trop Med Hyg 91:335-42.

17- Chekem L. and Wierucki S., 2007; Extraction of artemisinin and synthesis of its derivates artesunate and artemether .Médecine tropicale : revue du Corps de santé colonial 66(6):602-5.

18-Codex.The Pharmaceutical Codex, Principles and Practice of Pharmaceutics. Walter Lund. Direction of the Council of the Royal Pharmaceutical Society of Great Britain .London .1994.pages 277-310

19-Chinese Pharmacopoeia. Pharmacopeia of People Republic of china. Jinhua C.A.O., Xianghui G.U.O., Xianghui S.O.N.G., Xiaoyu T.A.N.G., He W.A.N.G .People's Medical Puplishing House. Vol. II. .1996.pages 40-41

20-Dayan, A. D., 1998. Neurotoxicity and artemisinin compounds do the observations in animals justify limitation of clinical use. Med Trop,58:32-7.

21-Dondorp A.M., Newton P.N., Mayxay M., Van Damme W., Smithuis F.M., Yeung S., Petit A., Lynam A.J., Johnson A., Hien T.T , McGready R., Farrar J.J., Looareesuwan S., Day N.P., Green M.D., White N J.,2004. Fake antimalarials in southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials . Trop Med Int Health 9:1241-1246.

22-David G.W., 1999. Pharmaceutical Analysis. Churchill livingstone. page 196-197.

23-DGP. General directorate of pharmacy, 2007. Artesunate100mg+SP and Artesunate 50mg+SP.General Secretary of Federal board of Pharmacy &Poisons. Committee no.29/2007.0403.

24-FDA, 2000. Analytical Procedures andMethods Validation: Chemistry, Manufacturing, and Controls, Federal Register (Notices) 65 (169), 52,776–52,777.

25-FDA, 2007. Post-marketing Safety Surveillance. P060021/A011, Section V, Clinical, Section 6.1-6.2, Pages 94-108.

26-Esimonea C.O., Okoyeb F.B.C., Onaha Nworuc B.U., Omejeb& E.O., 2008. In vitro bioequivalence study of nine brands of artesunate tablets marketed in Nigeria,. J Vector Borne Dis 45, 60–65.

27-Ema S., 2009.Specific quality problem with several categories of essential medicine-antimalarials.WHO. Interregional Seminar for Quality Control Laboratories involved in WHO Prequalification Programme and/or participating in respective sampling and testing projects, Nairobi, Kenya.

28-EMEA, 2000. Guideline for the conduct of post-marketing surveillance studies of veterinary medicinal products. The European Agency for Evaluation of Medicinal Product Veterinary Medicines and Information Technology. EMEA/CVMP/044/99.

29-Golenser J., Wakinine J.H., Krugliak M., Hunt N.H., Grau Georges E. ,2006.Vol. 36, no14, pp. 1427-144.

30-Gabriëls M.and Plaizier V. J., 2004. Experimental designed optimization and stability evaluation of dry suspensions with artemisinin derivatives for pediatric use, Pharmaceutics Vol.283, 19-34.

31-Gaudin K., Langlois M.H., Barbaud A., Boyer C., Millet P., Fawaz F., Dubost J.P., 2007.Stability of artesunate in pharmaceutical solvents. J Pharm Biomed Anal. 19; 43(3):1019-24.

32-ICH, 2000.International Conference on Harmonization; Draft Guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and Products: Chemical Substances," Federal Register (Notices) 65 (251), 83041–83063.

33-IP.The International Pharmacopoeia, Third edition, World Healt Organization, Geneva. Vol. 5, 2005,pages1007-1010.

34-IP, 2009.Draft revision for The International Pharmacopoeia. Draft for comment working document QAS/09.340 R ESTRICTED.WHO.

35-Indian pharmacopeia. Govermental of India Ministry of Health &Family Welfare. The Controller of Publications,Delhi.Vol.II.2009,page 65-62.

36-Jay B., Kevin J., and Pierre B., 2003. Understanding and Implementing Efficient Analytical Methods Development and Validation. Pharmaceutical Techn. Anal. Chemistry & Testing 6-13.

37-Jane P.,2005. WHO combats counterfeit malaria drugs in Asia. http://www.bmj.com/cgi/content/full/330/7499/1044-d. Retrieved on2007-06-15. Accessed 6Mars 2010.

38-János P., 2004. Quality management of antimalarial medicines-experience in prequalification of antimalarial medicines (product dossier assessment). WHO - Bangkok,pages 28-30.

39-Klayman D.L.,1985. Qinghaosu (artemisinin): an antimalarial drug from China. Sci 228:1049-55.

40-Li G. F., and Zhou Y. Q., 1989. Development of resistance to artemisinin (qinghaosu) and its derivatives by Plasmodium berghei, In S.Jiaxiang (ed.), Antimalarial drug development in China. National Institute Pharmaceutical Research and Development, Beijing, PR China, Beijing . 89-93.

41-Lindegårdh N., Dondorp A.M., Singhasivanon P., White N.J., Day N.P., 2007. Validation and application of a liquid chromatographic-mass

spectrometric method for determination of artesunate in pharmaceutical samples. J.Pharm. Biomed. Anal. 21; 45(1):149-53.

42-Lindegardh N., Tarning J., Toi P.V., Hien T.T., Farrar J, Singhasivanon P.,White N.J.,Ashton M., and Day N.P.J.,2009. Quantification of artemisinin in human plasma using liquid chromatography coupled to tandem mass spectrometry, J. Pharm .Biomed. Anal., 49(3): 768–773.

43-Manisha U. P. ,Vivek K. J.,Rajendra K. J.,Suraj S. D..andDattatray S. N., 2008. Simultaneous RP-LC Determination of Artesunate and Amodiaquine in Pharmaceutical Preparations. J. Chroma. Vol. 68, 8918-8926.

44-Malik E.M., Mohamed A., Elmardi1.K.A., Mowien1 R.M., Elhassan 1.A.H., Elamin1 S.B, Mannan 1. A.A., and Ahmed E.S.,2006. From chloro-quine to artemisinin-based combination therapy: the Sudanese experience. Malar J; 5: 65-68.

45-Malik E.M., andSaeed O.K., 2004;Malaria in Sudan: past, present and the future. Gazera J Health Sci , 1:47–53.

46-Mankil J., 1994.Current Development in the Chemistry of Artemi-sinin and Related Compounds. Current Medicinal Chemistry, 35-49.

47-Miller J.N., and Miller J.C., 2005.Statistics for Analytical Chemistry. Fifth edition. Pearson Education Limited, pages 19-51.

48-Newton P.N., Green M.D., Fernández F.M., Day N.J.P., White N.J., 2006. Counterfeit anti-infective medicines. Lancet In Dis.; 6:602–613.

49-Newton P.N., Green M.D., Proux S.,Smithuis F.,Rozendaal J.,2001.Fake artesunate in southeast Asia. Lancet 357:1948-1950.

50-Newton P.N., Lee S.J., Goodman C., Fernández F.M., Yeung S., Phanouvong S., Kaur H., Amin A., Whitty C.J.M., Kokwaro G., Lindegårdh N., Lukulay P., White L., Day N.P.J., Green M.D., White N.J., 2009.Guidelines for field surveys of the quality of medicines: PLoS Med.a proposa 6:e1000052. doi: 10.1371/journal.pmed.1000052

51-Navaratnam V.,Mansor S.M., Sit N.W.,Grace J., Li Q., Olliaro P., 2000. Pharmacokinetics of artemisinin-type compounds. Clin. Pharmacokin. 39(4):256- 270.

52-Obinna O., Harparkash K., Nkem D., Elvis S., Benjamin U., Kara H., Viola O., Paul O., 2009 .Quality of anti-malarial drugs provided by public and private healthcare providers in south-east Nigeria- Malar J 8:22.

53-Omer A.H.,1978. Response of Plasmodium falciparum in Sudan to oral chloroquine. Am J. Trop Med Hyg. 27:853–857.

54-Odunfa O.O., Adegoke O.A., and Onaga I.C., 2009. Pharmaceutical equivalence of some commercial samples of artesunate and amodiaquine tablets sold in South western Nigeria Trop.J.of Pharmaceutical Research, December; 8 (6): 491-499.

55-Presser.A., Buzzi S., 2009. Large-Acale Synthesis of Dihydroartemisinin and Artesunate .Sci pharm, 77:223.

56-Price R. M., van V., Nosten L. F.,Brockman C.,Phaipun L.A,. and White.N.,1998. Artesunate versus artemether for the treatment of recurdescent multi drug-resistant falciparum malaria. Am. J.Trop. Med.Hyg.59:883-8.

57-Price R. N., Nosten C. F., Luxemburger F. O., ter K. L. P. and White N. J.,1996. Effects of artemisinin derivatives on malaria transmit-ssibility. Lancet 347:1654-8.

58-PPRO, 2008. Republic of Sudan Federal Pharmacy &Poison board. The Ph-armacy and Poisons Act, and Regulations and 0rder.Item No.12 (6, 7).

59-Rodger W. S., Kenneth G. L., Peter M., Greg K., István P. ,and Christina K.,2009. High performance liquid chromatographic evaluation of artemisinin, raw material in the synthesis of artesunate and artemether . Kramld Journal of Chromatog. A.Vol. 1216, 8918-8925.

60-Richard H. K., 2007. Artesunate and Dihydroartemisinin (DHA): Unusual Decomposition Products Formed under Mild Conditions and Comments on the Fitness of DHA as an Antimalarial Drug, J Pharm Biomed Anal. Vol. 45 :149-153.

61-Robert G. R., 2003.To kill a parasite .Nature.Vol 424 , 887-889.

62-Remington's, 2005. Pharmaceutical Sciences, Paul B., Alfonso R .G., ,Ara D. M.,Linda F.,Steven G.,Pardeep G.,Nicholas P.,William R.,Randy H.Philadelphia College of Pharmacy and Science.pages 653-666

63-Stivanello E., Cavailler P., Cassano F., Omar S.A., Kariuki D., Mwangi J., Piola P.,Guthmann J.P., 2004, Efficacy of chloroquine, sulphadoxine-pyrimethamine and amodiaquine for treatment of uncomplicated Plasmodium falciparum malaria in Kajo Keji county, Sudan. Trop Med Int Health.; 9975–80.

64-Sivong S., Michael G. D., Facundo F. M., Manolin O.,Khamlieng P., Vongsavanh I., Christina H. Y., Leonard N., Dallas C .M., Dana H., Lamphet K., Latsamy V., Samlane P., Viengxay V., Lamphone S.,and Paul

N. N., 2009. A stratified random survey of the proportion of poor quality oral artesunate sold at medicine outlets in the Lao PDR – implications for therapeutic failure and drug resistance. Malar J. 8: 172.

65-Thekke V.S. and Badiadka N.,2009. Asimple and rapid spectrophotometric method for the determination of artesunate in pharmaceuticals. J. Anal. Chem. 4(1): 119-126.

66-Taylor R.B., Shakoor O., Behrens R.H., Everard M., Low A.S., Wangboonskul J., Reid R.G., Kolawole J.A.,2001. Pharmacopoeial quality of drugs supplied by Nigerian pharmacies. Lancet 357:1933–1936.

67-Tran T. H., Day N. P. H., Nguyen P., Nguyen T. H. , Pham P. L., Dinh X. S., Ly V. C., Ha D., Waller V., Peto T. E., and White N. J., 1996. A controlled trial of artemether or quinine in Vietnam adults with severe falciparum malaria .N Engl J Med 335:76-83. 22.

68-USP,2007. The United States Pharmacopeia. Convention ,INC. 12601 Twnbook Parkway, Rockville ,MD 20852. , 2007, (1225)&(711)

69-USP.2009.USP's Non-U.S. Standards Guideline. Draft 1- For Public Comment. The United State Pharmacopeia.

70-Van A., Eggeltem M.A.T.A.,and Van B.C. J., 1999. Artem-isinin drugs in the treatment of malaria: from medicinal herb to registered medication. Trends Pharmacol Sci 20:199-205.

71-Van Q., Soomro S.A, Cordonnier J.A.,and Jansen F.H., 2008.Optimization of an LC-MS method for determination of artesunate and dihydroartemisinin in plasma levels using liquid-liquid extraction .J.Anal.-Toxicol.32-133.

72-Van V., Angus B. , Price R., Mann C. S., J. A., Poletto C., Htoo S. E., Looareesuwan S., White N. J., and Nosten F., 2000. A case-control auditory evaluation of patients treated with artemisinin derivatives for multi drug-resistant Plasmodium falciparum malaria.Am J Trop Med Hyg 62:65-9.

73-Woodrow C.J., Haynes R.K., Krishna S. J., 2005. Artemisinins. Postgrad Med 81:71-78.

74-Woerdenbag H. J., Pras N., van Uden W. ,Wallaart T. E., Beekman A. C., and Lugt C.B., 1994. Progress in the research of artemisinin related antimalarials, an update. Pharm World Sci 16:169-80.

75-White N.J., 1994. Clinical pharmacokinetics and pharmacodynamics of artemisinin and derivatives. Trans R Soc Trop Med Hyg ; 88 Suppl 1:S41-3.

76-White N. J., Nosten F. , Looareesuwan S., Watkins W. M., Marsh K., Snow R.W., Kokwaro G., Ouma J., Hien T. T., Molyneux M. E. E.,Taylor T., Newbold C.I., RuebushT.K., Danis M., Greenwood B. M., Anderson R. M. and Olliaro P., 1999. Averting a malaria disaster. Lancet 353:1965-7.

77-White N. J., and Olliaro P., 1998. Artemisinin and derivatives in the treatment of un complicated malaria. Med Trop; 58:54-57

78-Winstanley P. A., 2000. Chemotherapy for falciparum malaria: the armory, the problems and the prospects. Parasitol Today 16:146-53.

79-White N.J., 2004. Antimalarial drug resistance. J. Clin. Invest. 113 (8): 1084–1087.

80-WHO, 1999. Guidelines for the development of measures to combact counterfeit drugs. DMP-DAP Joint Project on Counterfeit Drugs. World Health Organization, Geneva (WHO/EDM/QSM/99.1).

81-WHO, 2001.World Health Organization .Antimalarial drug combination therapy. Report of a WHO Technica Consultation.WHO/CDS/RBM/2001-.35.

82-WHO, 2003.Fake artesunate tablets circulating again. WHO Drug Information Vol.17, No.2.

83-WHO, 2003.An Update on Quality Assurance and Procurement through WHO for Improving Access to Artemisinin-Based Combination Treatments (ACTs) for Malaria Control Department World Health Organization, Geneva.

84-WHO, 2003.World Health Organization Geneva, Expert Committee on Specification for Pharmaceutical Preparations. World Health Organization Geneva .Thirty –seven Report. Technical report series 908. Annex 3&4.

85-WHO, 2003, World Health Organization Geneva: Improving Access to Antimalarial Medicines - Roll Back Malaria Partnership Meeting (in press). Geneva: WHO.) L/2003.1095 (ed. H Haak).

86-WHO, 2004.World Health Organization Geneva Quality assurance of pharmaceuticals A compendium of guidelines and related materials, Updated edition Good manufacturing practices and inspection. Analytical method. Volume 2, Appendix 4.

87-WHO, 2005. Malaria control today: Current WHO Recommendations. RBM Department; Geneva.

88-WHO, 2007. Stability testing of active pharmaceutical ingredient and finish product. World Health Organization Geneva. Forty-third Report. Technical report series 953. Annex 2.

89-WHO, 2007. Access to artemisinin-based a medicinal product of acceptable quality-. Prequalification Programs.

90-WHO, 2009.Testing of active pharmaceutical ingredient and pharmaceuticals product. World Health Organization. Working document QAS/06.179-/Rev.1

91-WHO,2009.WHO Expert Committee on Specifications for Pharmaceutical Preparations Forty-third report. World Health Organization .Technical Report Series 953. 42-54

92-Yang C., Shi-Min Z., Hong-Yuan C., Ying L.,1998.Bioelectro-chemistry and Bioenergetics 44,295-300.

Chapter 7
Appendix

Table No. (1): Results of analysis of post -marketing surveillance of artesunate tablets (AS+SP) for adults in Khartoum

Dosage form	Product	Round 1		Round 2		Round 3		Round 4		Round 5		Round 6	
		Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content % (w/w)
Artesunate for Adult	Artesumie	98.59 ±1.2	103.97±0.4	96.00±1.1	99.68±0.33	94.02±2.1	102.19±0.4	85.68±1.1	103.47±0.3	89.8±3.3	100.8±0.4	91.6±1.3	101.5±0.4
		95.45±0.99	99.62±0.43	96.51±1.2	98.42±0.4	82.51±4.1	99.36±0.34	90.84±2.1	109.68±0.4	93.2±3.2	99.13±0.8		
		95.96 ±2.1	97.93 ±0.5	97.75±2.3	101.00±0.6			83.93±3.1	101.14±0.8				
				98.32±0.9	100.3±0.5								
	Ariplus	66.09±0.98	96.23±0.33	61.49±2.4	98.43±0.3								
		59.54±3.1	99.71±0.67	64.89±1.1	100.95±0.9								
		62.39 ±2.3	100.5±0.77	69.92±1.1	96.82±0.66								
		67.47± 2.2	97.37±0.45	60.88±2.5	98.44±0.4								
				52.84±1.3	97.2±0.8								
				55.71±4.1	98.5±0.4								
	Artemal			80.38±3.1	98.89±0.7	91.43±2.4	96.30±0.5	91.03±3.2	101.12±0.3	76.6±2.1	95.1±0.4	84.05±08	96.08±0.5
				84.41±2.1	96.18±0.5	83..84±07	97.97±0.6	79.40±2.1	95.65±0.5			80.44±07	96.83±0.7
				86.21±3.1	95.7±0.44								
	Combisuate					59.32±1.2	94.27±0.5						
						54.71±2.3	89.40±0.6						
						52.90±2.5	87.46±0.7						
	ASP							79.74±4.1	96.22±0.5	82.0±2.7	97.22±0.4	80.8±3.1	98.93±0.3
								80.00±1.9	98.99±0.3	74.1 ±3.2	94.44±0.7	81.7±0.9	100.3±0.8
								65.45±2.5	98.08±0.5	73.4±1.3	95.09±0.5	81.2±3.8	95.00±0.5
								61.64±2.2	94.00±0.7			80.8±1.9	96.60±0.3

IP requirement: 90-110 of amount stated on label (n=3);[b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%) .
[d]n=6 IP requirement for dissolution test >60%

Table No. (2): Results of analysis of post -marketing surveillance of artesunate tablets (AS+SP) for children in Khartoum

Dosage form	Product	Round 1		Round 2		Round 3		Round 4		Round 5		Round 6	
		Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content % (w/w)	Drug rel % 30 min[b].	[a]Content % (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)
Artesunate for children	Artesumie	95.17 ±2.3	100.62±0.7			95.13±2.3	105.63±0.6	91.77±2.3	104.61±04	88.70 ± 0.9	102.21±0.5	92.37±2.2	98.10±0.3
		94.71 ±1.1	99.96±0.43			96.18±0.9	98.85±0.8	91.76±3.3	101.6±0.6	93.45 ± 1.1	96.98±0.4	92.57±1.4	94.69±0.5
								92.02±1.8	105.26±04	94.22 ±4.1	101.57±0.3		
	Ariplus	47.96 ±3.5	107.11±0.5	45.68±2.5	98.2±0.43								
		50.29 ±2.2	100.89±0.7	43.79±2.3	100.09±0.4								
		50.59± 1.4	100.33±0.6	81.02±1.4	93.16±.06								
		80.87±4.1	97.00±0.34	45.08±0.9	98.17±0.5								
	Artemal			89.90±1.5	95.01±0.50	90.91±1.9	97.33±0.5	94.61±1.1	109.5±0.8	82.08±2.1	97.44±0.6	84.13±2.1	100.12±0.6
				89.97±2.2	96.00±0.6	90.43±2.7	96.68±0.4						
				90.83±0.9	94.64±0.44	92.91±0.9	98.73±0.3						
	ASP					91.03±3.1	94.92±0.4						
								66.82±2.3	97.65±0.3	68.25 ±2.2	93.69±0.3	92.12±1.0	101.23±0.5
								79.08±1.5	99.46±9.5	87.32 ±1.9	98.3±0.5	83.91±1.1	100.55±0.3
										84.07 ±1.7	96.26±0.3	84.41±2.4	94.81±0.4
										67.58 ±1.5	93.78±0.6	82.86±2.4	97.46±0.7
												69.87±4.1	94.29±0.6
												67.75±2.3	96.96±0.4

IP requirement: 90-110 of amount stated on label (n=3);[b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6 IP requirement for dissolution test >60%

Table No. (3): Results of analysis of post -marketing surveillance of artesunate tablets (AS+SP) for adults in Elgadarif

Dosage form	Product	Round 1		Round 2		Round 3		Round 4		Round 5		Round 6	
		Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)
Artesunate for Adult	Artesumine	95.55±1.5	103.41±0.33	96.66±2.1	98.54±0.33	94.27±1.8	108.06±0.7	-----	-----	81.63 ±2.1	98.64±0.9	90.83±0.9	100.60±0.4
		98.81±2.3	100.77±0.43	94.18±1.3	100.74±0.5	96.23±1.7	101.47±0.4	-----	-----	86.67± 0.9	99.96±0.3	93.15±3.2	99.44±0.8
								-----	-----	87.08 ±0.8	99.06±0.30.		
	Ariplus	53.18±1.9	99.98±0.46	71.14±1.1	95.81±.0.45			-----	-----				
		56.78±3.1	101.12±0.66	59.69±1.4	99.74±0.6			-----	-----				
		56.09±3.3	98.84±0.44	62.56±2.1	95.49±0.4			-----	-----				
		54.64±2.3	98.02±0.46	53.71±0.8	91.49±0.6			-----	-----				
		57.01±1.5	98.82±0.71					-----	-----				
	Artemal			94.25±1.7	96.48±0.4			-----	-----	69.6± 0.9	97.3±0.5	65.98±1.1	93.60±0.6
				89.27±0.8	101.78±0.5			-----	-----	69.01± 4.2	98.5±0.8		
				95.47±2.1	98.25±0.7			-----	-----				
	Artescope					92.19±0.9	100.87±0.4	-----	-----	88.70±2.1	99.64±0.4	101.24±2.0	103.56±0.4
						90.27±0.9	105.21±0.8	-----	-----	85.52±1.3	97.84±0.3	92.03±3.7	99.32±0.3
						90.84±2.2	99.69±0.4	-----	-----	83.68±2.5	98.00±0.6		
						89.78±3.2	100.04±0.3	-----	-----	84.60±2.2	98.68±0.4		
	Combisunate					49.48±1.5	94.11±0.9	-----	-----				
						53.70±1.4	90.55±0.8	-----	-----				
						53.53±2.1	89.92±0.4	-----	-----				
						55.23±1.1	91.40±0.6	-----	-----				
	ASP							-----	-----	69.35± 1.2	98.05±0.6	67.27±0.9	93.60±0.5
								-----	-----	68.62 ±2.2	96.27±0.7	76.00±1.1	94.56±0.4

IP requirement: 90-110 of amount stated on label (n=3);[b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6 IP requirement for dissolution test >60%
. .----=This round not done

Table No. (4): Results of analysis of post -marketing surveillance of artesunate tablets (AS+SP) for children in Elgadarif

Dosage form	Product	Round 1		Round 2		Round 3		Round 4		Round 5		Round 6	
		Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)
Artesunate for children	Artesumine	96.90± 1.2	98.92±0.54	96.65±2.1	107.32±0.6	91.46±1.1	104.21±0.4	-----	-----	95.5± 1.1	97.0±0.5	100.1±3.3	102.46±0.9
		97.07±0.99	103.17±0.77	95.40±3.1	99.60±0.43	100.63±3.1	98.41±0.7	-----	-----	100.66± 0.7	101.40.±0.6		
				101.5±3.2	103.74±0.8	90.48±1.5	102.62±0.4	-----	-----	99.7± 0.6	100.8±0.3		
				95.63±1.1	103.13±0.4			-----	-----				
				94.15±1.4	100.96±0.4			-----	-----				
				95.40±0.9	104.43±0.8			-----	-----				
				99.98±0.8	103.57±0.6			-----	-----				
	Ariplus	41.66±0.99	100.02±0.5	45.53±1.5	93.04±0.8			-----	-----				
		41.0±0.98	101.61±0.6					-----	-----				
		48.75±3.1	101.3±80.34					-----	-----				
		42.02±0.89	99.89±0.4					-----	-----				
		39.91±2.4	100.25±0.6					-----	-----				
	Artemal			93.06±1.1	101.53±0.3	85.16±2.1	101.18±0.3	-----	-----	75.32 ±1.1	93.99±-0.3	83.59 ±2.1	97.42 ±0.3
				93.81±0.7	100.67±0.7	94.57±2.2	104.66±0.4	-----	-----				
	Artescope					100.03±1.4	103.12±0.6	-----	-----	97.61± 3.2	99.5±0.7	97.92±1.6	100.21±0.4
						94.90±1.3	99.67±0.4	-----	-----	94.71±3.1	101.56±0.3	95.25±1.2	101.34±0.5
						99.00±2.3	100.00±0.7	-----	-----	94.25± 4.1	98.56±0.4	94.5±1.3	98.87±0.3
						97.25±2.1	105.20±0.7	-----	-----	93.44 ±3.5	101.18±0.3		
								-----	-----	99.35± 1.1	100.5±0.6		
	ASP							-----	-----			81.54±3.2	99.72±0.6

IP requirement: 90-110 of amount stated on label (n=3);[b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6 IP requirement for dissolution test >60%
.----=This round not done

Table No. (5): Results of analysis of post -marketing surveillance of artesunate tablets (AS+SP) for adults in Atbara

Dosage form	Product	Round 1		Round 2		Round 3		Round 4		Round 5		Round 6	
		Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content % (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)
Artesunate for Adult	Artesumine	97.50±1.2	95.51 ±0.3	75.56±1.1	99.20 ±0.6	89.59±2.3	101.89±0.6	73.65±4.1	96.19±0.3	91.34 ±0.9	102.62±0.7	93.61±2.0	101.55±0.4
		96.90±0.90	95.51± 0.6			98.38±3.2	102.38±0.4	90.0 ±2.3	99.01±0.4				
		93.10 ±1.6	92.42± 0.4										
	Ariplus	56.47± 2.2	97.23±0.44	42.33±2.4	97.80±0.33								
		62.08 ±1.8	93.11±0.36	48.06±3.1	96.81±0.8								
				47.13±4.1	102.27±0.6								
				52.33±2.2	98.21±0.5								
				54.73±0.9	99.72±0.4								
	ASP							75.99±2.2	97.18±0.3	70.33 ±4.1	98.39±0.6	67.12±3.3	103.06±0.3
								70.49±4.1	101.6±0.4	74.62 ±1.1	97.74±0.4	69.60±2.2	99.33±0.7
								68.27±3.3	95.27±0.3	73.87 ±3.1	97.19±0.4	78.65±2.3	95.33±0.6
								68.11±1.3	96.74±0.5				
	Artema			77.57±2.5	98.58±0.5	94.38±1.1	101.6±0.5	82.83±2.3	95.6±0.6				
				96.50±2.3	98.23±0.4	93.61±3.2	98.98±0,3	81.17±2.2	98.36±0.3				
								77.88±1.5	101.4±0.6				
	Combisunate					53.14±0.9	86.19±0.3						
						47.82±1.8	92.21±0.6						
						49.52±0.9	93.21±0.7						
						51.29±2.2	93.21±0.4						
	Artecosp									92.40 ±2.1	100.10±0.7	91.9±30.9	97.07±0.4
										94.82± 2.2	99.78±0.5	94.92±0.8	103.02±-.6
										91.27 ±1.6	101.61±0.4	89.62±3.2	98.34±0.4
												91.72±4.1	103.22±0.5

IP requirement: 90-110 of amount stated on label (n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6 IP requirement for dissolution test >60%

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Table No. (6): Results of analysis of post -marketing surveillance of artesunate tablets(AS+SP) for children in Atbara

Dosage form	Product	Round 1		Round 2		Round 3		Round 4		Round 5		Round 6	
		Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)
Artesunate for children	Artesumine	98.2±3.1	99.48 ±0.8	100±1.4	102.32±0.4	94.61±4.1	94.84±0.6	80.43±3.4	97.77±0.8	96.27 ±1.9	99.59±0.5	99.38±1.9	101.43±0.5
						95.75±2.4	100.89±0.8						
						103.61±3.3	104.24±0.3						
	Ariplus	50.11±1.9	98.58±0.33	94.59±0.8	100.79±0.23								
		45.35±0.88	91.49 ±0.4	44.82±1.3	97.27±0.6								
		47.76±0.97	100.09±0.7	41.72±2.1	97.76±0.6								
				45.73±1.5	101.19±0.7								
	Artemal			93.00±1.9	96.75±0.33	100.18±2.2	107.04±0.7	90.85±1.9	95.06±0.5	91.08 ±2.8	98.38±0.5	81.58±2.7	93.96±0.3
						96.19±3.1	102.59±0.6	93.93±4.2	100.34±0.7			92.80±1.8	94.34±0.6
						91.01±1.4	103.08±0.5	90.95±2.2	95.16±0.4				
	ASP							70.87±1.1	99.83±0.6	82.87 ±2.2	96.63±0.5	76.60±3.1	96.70±0.5
								77.98±1.3	96.69±0.4	82.89± 2.3	94.01±0.3	78.92±4.1	95.40±0.3
								62.81±2.1	99.96±0.5	75.83± 2.2	94.83±0.3	85.20±3.5	97.31±0.9
								73.04±0.9	96..36±0.8				
	Artecosp									80.08 ±1.8	91.50±0.8	95.56±0.9	100.74±0.7
										101.45±3.2	102.57±0.3	99.0±2.2	99.29±o.3
										93.24 ±3.1	104.02±0.5	98.48±3.0	100.96±0.3
												103.06±2.2	104.19±0.4

IP requirement: 90-110 of amount stated on label (n=3);[b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6 IP requirement for dissolution test >60%

Table No. (7): Results of analysis of post -marketing surveillance of artesunate tablets (AS+SP) for adults in Elobied

Dosage form	Product	Round 1		Round 2		Round 3		Round 4		Round 5		Round 6	
		Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)
Artesunate for Adult	Artesumine	96.79±3.2	100.63±0.44	96.07±1.3	96.42±0.5	82.43±3.1	98.00±0.7	84.75±1.1	102.0±0.7	93.31±1.8	98.16±0.3	87.49±1.5	100.22±0.4
				96.58±2.2	97.95±0.7	89.97±4.1	102.14±0.3	94.99±2.1	98.61±0.3	88.58±2.2	98.40±0.8	95.22±4.2	98.02±0.3
				98.71±2.3	99.33±0.8								
	Ariplus	57.04±1.9	98.33±0.5	52.79±1.1	96.16±0.8								
		58.21±1.9	99.17±0.6										
	artemal			92.77±0.9	95.62±0.6	96.45±0.9	101.32±0.4			81.78±4.1	99.43±0.2		
				83.61±2.2	93.82±0.3								
				84.29±3.2	90.68±0.7								
	Artecosp					90.74±1.0	99.60±0.3	86.66±1.4	100.13±0.3	94.82±0.3	100.29±2.1	98.8±2.2	99.97±0.4
						92.04±2.1	102.14±0.4	90.3±1.2	97.83±0.6	91.24±2.1	97.59±0.9	96.72±1.9	99.97±0.6
						94.11±2.2	100.50±0.6	99.05±1.1	100.33±0.4	95.09±1.5	96.65±0.5		
						101.33±1.3	107.80±0.7	90.0±0.9	97.78±0.7	91.59±1.6	96.29±0.6		
						93.77±1.4	100.50±0.7						
	ASP							59.77±3.2	96.34±0.7	79.56±0-9	96.53±0.6	73.73±2.1	97.97±0.8
								59.61±4.1	94.13±0.4	75.47±1.7	93.23±0.7	76.64±3.2	98.70±0.3

IP requirement: 90-110 of amount stated on label (n=3);[b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6 IP requirement for dissolution test >60%. .

Table No. (8): Results of analysis of post -marketing surveillance of artesunate tablets (AS+SP) for children in Elobied

Dosage form	Product	Round 1		Round 2		Round 3		Round 4		Round 5		Round 6	
		Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)	Drug rel % 30 min[b].	[a]Content% (w/w)
Artesunate for children	Ariplus	46.03±0.99	97.72±0.35	46.32±3.1	95.72±0.4								
		40.03±1.4	100.0±0.77										
		49.29±4.1	100.50±0.67										
	Artesumine			93.55±1.4	95..55±0.33	87.61±1.1	101.10±0.8	86.56±2.2	100.27±0.3	100.15±4.1	105.81±0.9	91.37±4.0	100.20±0.4
				96.51±1.5	98.53±0.5	97.11±2.2	104.18±0.6	95.45±2.1	100.58±0.4	96.79±1.1	98.16±0.2	91.34±3.0	98.5±0.9
				98.31±3.1	98.35±0.7			90.87±2.2	100.3±0.6	96.13±2.2	99.08±0.4	95.59±3.2	102.22±0.7
				96.72±2.1	97.73± 0.4								
	Artemal			89.1±1.70	94.98±0.8	91.682.2	97.03±0.3	96.91±3.1	98.20±0.4	86.92±3.1	92.9±0.3	82.59±1.1	98.27±0.5
				88.39±1.9	94.71±0.6			86.1±3.3	96.49±0.5	81.14±1.1	101.92±0.4		
								88.6±3.4	97.03±0.7				
	Artecosp					100.8±0.3	101.70±0.3	95.05±2.4	97.42±0.4	90.13±2.3	97.06±0.3	92.0±2.2	96.94±0.6
						95.42± 2.3	102.20±0.4	98.7±2.2	99.62±0.3	96.11±1.5	95.96±0.6	93.73±3.7	95.35±0.5
						96.80±1.6	105.23±0.9	94.72±1.7	98.69±0.5	95.79±2.2	96.72±0.2	96.68±0.9	98.27±0.8
						94.54±3.1	104.1±0.5	98.71±1.9	99.89±0.3	91.66±3.3	98.62±0.2		
						101.51±1.1	105.21±0.6						
	ASP									75.01±2.8	97.9±0.8	84.73±3.3	93.63±0.6
										86.25±1.1	93.23±0.3	75.75±2.2	95.01±0.9

IP requirement: 90-110 of amount stated on label (n=3);[b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6. IP requirement for f dissolution test >60%.

Table No. (9): Results of analysis of the stability study of Artesumine tablets for children at room temperature in Khartoum

Time (month)	[a]Content%(w/w)			Drug rel % 30 mn[b].			Degradation products		
	Batch No. LS061201	Batch No. LS060401	Batch No. LS060601	Batch No. LS061201	Batch No. LS060401	Batch No. LS060601	Batch No. LS061201	Batch No. LS060401	Batch No. LS060601
Zero	102.0±0.44	100.9±0.70	106.3±0.77	98.3±2.83	89.0±1.12	104.0±1.8	Not detected		
3 months	101.4±0.16	99.0±0.71	105.0±0.50	98.0±1.01	88.3±1.40	104.0±1.3	detected		
6 months	100.7±0.06	98.9±0.46	104.1±0.82	97.9±1.07	87.7±1.20	102.9±2.0	detected		
9 months	99.0±0.01	98.0±0.32	103.3±0.40	96.9±1.22	87.5±1.77	103.1±3.8	detected		
12 months	98.92±0.34	98.1±1.64	102.1±0.60	95,1±1.56	96.9±1.50	102.7±3.9	detected		
18 months	98.0±0.77	97.8±0.33	101,7±0.33	94.3±0.90	96.5±3.0	101.6±1.0	detected		
24 months	97.92±0.65	97.0±0.88	100.4±0.90	94.1±1.70	96.3±0.98	100.9±0.9	detected		
36 months	96.70±1.60	96.2±0.28	100.00±1.11	93.00±3.2	85.1±1.66	100.0±3.7	detected		

IP requirement:90-110 of amount stated on label(n=3);bn =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)

IP requirement for dissolution test >60%

Table No. (10): Results of analysis of the stability study of Artesumine tablets for adults at room temperature in Khartoum

Time (month)	[a]Content%(w/w)			Drug rel % 30 mn[b].			Degradation products		
	Batch No. LS060602	Batch No. LS060301	Batch No. LS060401	Batch No. LS060602	Batch No. LS060301	Batch No. LS060401	Batch No. LS060602	Batch No. LS060301	Batch No. LS060401
Zero	102.07±0.77	101.9±0.3	104.9±0.33	97.42±0.8	95.6±1.2	98.5±2.0	Not detected		
3 months	100.3±0.6	100.0±0.8	103.8±0.4	96.9±1.5	95.0±1.4	98.1±4.1	detected		
6 months	100-0±0.3	100.0±0.4	103.0±0.5	94.4±0.6	96.4±2.8	96.4±3.9	detected		
9 months	99.8±0.5	99,8±0.66	102.1±0.6	95.02±4.9	95.1±4.7	97.0±1.0	detected		
12 months	98.5±0.8	98.3±0.8	101.0±0.6	93.7±2.9	94.8±1.9	96.1±0.9	detected		
18 months	97.8±0.6	97.1±0.9	100.3±0.3	93.2±4.1	93.2±0.88	95.2±1.3	detected		
24 months	97.8±0.9	96.3±0.4	98.1±0.77	92.4±1.2	91.2±1.4	94.90±4.1	detected		
36 months	96.89±0.33	96.7±0.35	97.5±0.3	92.0±1.1	90.2±1.9	94.00±5.2	detected		

IP requirement:90-110 of amount stated on label(n=3);bn =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)

IP requirement for dissolution test >60%

Table No. (11): Results of analysis of the stability study of Artesumine tablets for children at room temperature in Port Sudan

Time (month)	[a]Content%(w/w)			Drug rel % 30 mn[b].			Degradation products		
	Batch No. LS061201	Batch No. LS060401	Batch No. LS060601	Batch No. LS061201	Batch No. LS060401	Batch No. LS060601	BatchNo.0 LS061201	Batch No LS060401	Batch No. LS060601
Zero	102.0±0.33	100.9 ±0.4	106.3±0.3	98.3±3.2	89.0±2.1	104.1±4.1	Not detected		
3 months	101.05±0.8	100.4±0.6	105.0±1.1	97.8±3.2	89.0±1.5	103.6±2.2	detected		
6 months	101.0±0.7	100.1±1.0	103.9±0.1	97.2±3.7	87.1±1.1	102.9±0.9	detected		
9 months	100.3±0.5	99.2±0.3	102.2±0.4	96.0±1.1	86.9±3.1	101.0±2.1	detected		
12 months	99.0±0.4	98.7±0,3	101.0±0,12	95.8±1.9	86.3±0.8	100.3±2.0	detected		
18 months	98.5±0.33	97.2±1.0	100.4±0.2	95.2±4.2	85.2±2.0	100.0±2.6	detected		
24 months	98.14±0.7	96.30±0.4	99.01±0.06	94.4±3.1	84.9±1.3	100.0±1.1	detected		
36 months	96.22±.0.55	95.80±0.9	97.20±0.04	93.5±0.8	84.20±1.8	99.3±2.1	detected		

IP requirement:90-110 of amount stated on label(n=3);bn =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)

IP requirement for dissolution test >60%

Table No. (12): Results of analysis of the stability study of Artesmine tablets for adults at room temperature in Port Sudan

Time (month)	[a]Content%(w/w)			Drug rel % 30 mn[b].			Degradation products		
	Batch No. LS060602	Batch No. LS060301	Batch No. LS060401	Batch No. LS060602	Batch No. LS060301	Batch No. LS060401	Batch No. LS060602	Batch No. LS060301	Batch No. LS060401
Zero	102.07±0.47	101.9±0.34	104.9±0.4	97.42±0.30	95.60±4.20	98.5±1.9	Not detected		
3 months	100±0.66	101,0±0.77	103.2±0.66	96-80±0.34	95.30±1.80	98.2±1.3	detected		
6 months	100.01±0.34	101.4±0.44	102.9±0.50	95.1±3.80	95.00±4.20	97.0±2.0	detected		
9 months	99.4±0.62	100. 9±0.9	101.0±0.40	94.0±5.0.	94.20±1.90	96.6±3.8	detected		
12 months	97.6±0.34	99.8±0.3	100.0±0.44	90.32±101	93.30±0.80	96.0±3.9	detected		
18 months	98.31±0.44	98.3±0.50	99.3±0.35	88.9±1.9	92.10±2.30	95.1±1.0	detected		
24 months	96.4±0.53	97.7±1.00	98.0±0.70	91.88±3.6	90.90±0.60	94.0±1.4	detected		
36 months	95.66±0.50	96.0±0.44	96.8±0.60	90.90±3.1	90.90±1.90	93.8±2.2	detected		

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement <1.0%)

IP requirement for dissolution test >60%

Table No. (13): Results of analysis of the stability study of Artesumine tablets for children at room temperature in Atbara

Time (month)	[a]Content%(w/w)			Drug rel % 30 mn[b].			Degradation products		
	Batch No. LS061201	Batch No. LS060401	Batch No. LS060601	Batch No. LS061201	Batch No. LS060401	Batch No. LS060601	Batch No. LS061201	Batch No. LS060401	Batch No. LS060601
Zero	102.0±0.33	100.9 ±0.8	106.3±0.6	98.3±2.11	89.0±0.98	104.1±3.90	Not Detected		
3 months	101.9±0.7	100.8±0.3	106.2±0.3	98.1±0.90	88.9.0±1.5	104.6±1.20	Not Detected		
6 months	101.0±0.5	100.11±0.9	106.5.0±0.9	97.9±3.1	87. ±3.00	104.1±0.50	Not Detected		
9 months	100.3±0.06	100.0±0.6	105.4±1.33	96.2±1.1	86.9±1.0	103.80±3.10	Not Detected		
12 months	100.0±0.3	99.70±0.7	104.9±0.9	95.8±0.99	86.0±1.80	103.10±1.40	Not Detected		
18 months	99.6±0.09	99.0±0.25	103.0±1.01	94.1±2.20	85.6±0.99	102.90±1.80	Not Detected		
24 months	99.0±0.77	98.20±0.4	102.2±0.6	92.1±3.10	84.9±2.2	102.30±4.20	Detected		
36 months	99.0±0.4	98.0±0.29	101,0±0.2	89±1.10	84.0±0.96	99.00±3.20	Detected		

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)

IP requirement for dissolution test >60%

Table No. (14): Results of analysis of the stability study of Artesumine tablets for adults at room temperature in Atbara

Time (month)	[a]Content%(w/w)			Drug rel % 30 mnb.			Degradation products		
	Batch No. LS060602	Batch No. LS060301	Batch No. LS060401	Batch No. LS060602	Batch No. LS060301	Batch No. LS060401	Batch No. LS060602	Batch No. LS060301	Batch No. LS060401
Zero	102.07±0.2	101.9±0.2	104.9±1.0	97.42±3.3	95.6±3.2	98.5±0.9	Not Detected		
3 months	100.9±0.1	101.1±0.8	104.0±0.3	97.0±4.4	95.2±1.1	97.9±2.1	Not Detected		
6 months	101.10±0.4	101.0±0.12	103.8±0.5	96.3±1.9	94.0±0.9	96.4±2.8	Not Detected		
9 months	100.0±0.4	100.9±0.55	102.7±0.67	95.0±0.9	92.9±1.9	95.2±2.0	Not Detected		
12 months	99.6±0.5	100.1±0-21	101.9±0.3	88.6±3.7	91.2±3.1	94.8±4.1	Not Detected		
18 months	98.0±0.3	99.3±0.4	101.0±0.9	91.9±1.1	90.1±3.1	93.0±0.9	Not Detected		
24 months	98.2±0.2	98.2±0.61	100.2±1.0	92.2±2.1	88.0±2.0	91. 9±1.2	Detected		
36 months	97.02±0.5	97.4±0.2	99.0±1.4	90.0±4.0	86.0±1.2	88.7±1.2	Detected		

IP requirement:90-110 of amount stated on label(n=3);[b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement:<1.0%)

IP requirement for dissolution test >60%

Table No. (15): Results of analysis of the stability study of Artesumine tablets for children at room temperature in Elobied

Time (month)	[a]Content%(w/w)			Drug rel % 30 mnb.			Degradation products		
	Batch No.0 LS061201	Batch No LS060401	Batch No. LS060601	Batch No.0 LS061201	Batch No LS060401	Batch No. LS060601	Batch No.0 LS061201	Batch No LS060401	Batch No. LS060601
Zero	102.0±0.33	101.9±0.4	106.3±0.2	98.3±3.4	89.0±3.01	104.1±2.1	Not Detected		
3 months	101.0±0.6	101.5±0.5	106.1±1.0	97.3±2.2	88.0±0.9	104.1±2.2	Not Detected		
6 months	100.8±1.1	101.0±0.2	105.8±0.3	96.9±0.9	87.1±1.5	1o4.1±1.8	Not Detected		
9 months	100.0±0.7	100.0±0.8	104.1±0.8	96.0±0.5	86.9±2.11	103.8±0.78	Detected		
12 months	99.5±0.2	99.0±0.4	102.9±1.0	95.2±2.1	85.9±0.9	103.0±0.9	Detected		
18 months	99.2±0.4	98.91±0.3	102.0±0.3	94.1±3.1	84.1±4.1	102.1±3.1	Detected		
24 months	98.8±0.5	98.2±0.3	101.3±0.3	92.8±0.9	83.9±2.2	101.2±3.8	Detected		
36 months	97.2±1.0	97.0±0.4	100. ±0.5	91.9±3.3	82.3±1.9	99.7±1.5	Detected		

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement <1.0%)

IP requirement for dissolution test >60%

Table No. (16): Results of analysis of the stability study of Artesumine tablets for adult at room temperature in Elobied

Time (month)	[a]Content%(w/w)			Drug rel % 30 mnb.			Degradation products		
	Batch No. LS060602	Batch No. LS060301	Batch No. LS060401	Batch No. LS060602	Batch No. LS060301	Batch No. LS060640	Batch No. LS060602	Batch No. LS060301	Batch No. LS060401
Zero	102.07±0.27	101.9±0.4	104.9±0.50	97.42±1.90	95.60±3.10	98.5±3.3	Not Detected		
3 months	101.00±0.50	100.18±0.40	104.50±1.00	96.70±2.10	95.00±1.30	98.5±1.4	Not Detected		
6 months	100.90±1.00	101.50±0.30	104.8±0.66	95.00±3.30	94.90±0.80	97. 0±2.0	Not Detected		
9 months	100.00±0.40	101.00±1.00	103.00±0.38	95.00±1.80	93.00±0.90	96.4±2.5	Detected		
12 months	100.00±0.20	100.20±0.70	102.60±0.55	94.40±1.60	93.50±1.00	95.5±2.0	Detected		
18 months	99.60±1.00	99.10±0.44	101.30±0.30	93.10±2.30	92.00±1.40	94.9±1.9	Detected		
24 months	98.70±0.60	98.00±0.30	99.80±0.22	91.20±0.80	91.20±3.30	93.8±3.8	Detected		
36 months	97.80±0.5	97.20±0.5	98.00±0.70	90.63±0.90	89.60±1.90	93.0±1.1	Detected		

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement <1.0%)

IP requirement for dissolution test >60%

Table No. (17): Results of analysis of Artesumin tablets for adults at room temperature in NDQCL

Time (month)	[a]Content%(w/w)		Drug rel % 30 min[b].		Degradation products	
	Batch No. 040801	Batch No 041201	Batch No. 040801	Batch No 041201	Batch No. 040801	Batch No 041201
Zero	105.40±0.66	101.5±0.35	100.80±1.41	96.5±1.77	Not detected	
3 months	104.01±0.40	100.91±0.30	100.00±3.30	96.10±2.30	detected	
6 months	103.92±0.23	100.20±0.23	99.40±2.10	95.64±3.10	detected	
9 months	101.80±0.80	100.00±0.80	99.80±1.10	94.88±1.16	detected	
12 months	100.10±0.45	99.10±0.45	99.00±3.5	95.0±3.20	detected	
18 months	100.80±0.33	99.80±0.33	98.00±2.1	95.9±1.21	detected	
24 months	101.00±0.79	98.30±0.79	97.2±0.90	93.62±0.90	detected	
36 months	100.40±0.55	97.00±0.33	97.00±1.70	92.66±1.87	detected	

IP requirement:90-110 of amount stated on label(n=3);[b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
IP requirement for dissolution test >60%

Table No. (18): Results of analysis of Artesumin tablets for children at room temperature in NDQCL

Time (month)	[a]Content%(w/w)		Drug rel % 30 min[b].		Degradation products	
	Batch No. 04081	Batch No. 04091	Batch No. 04081	Batch No. 04091	Batch No. 04081	Batch No. 04091
Zero	103.80±0.43	101.40±0.3	98.70±1.2	90.70±1.8	Not detected	
3 months	102.70±0.30	100.70±0.60	99.10±0.9	88.10±2.9	detected	
6 months	I00. 00±0.40	99. 00±0.50	97.30±1.7	87.30±3.7	detected	
9 months	99.60±0.60	98.60±0.30	97.00±0.88	87.00±0.98	detected	
12 months	98.00±0.52	97.00±0.72	96.00±2.40	86.00±2.70	detected	
18 months	97.80±0.50	96.80±0.40	95.60±1.9	85.60±0.9	detected	
24 months	96.90±0.43	96.00±0.63	93.90±3.1	84.90±2.3	detected	
36 months	95.40±0.76	95.40±0.46	91.90±1.4	84.10±1.6	detected	

IP requirement:90-110 of amount stated on label(n=3);[b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement:<1.0%)
IP requirement for dissolution test >60%

Table No. (19): Results of analysis of Ariplus tablets for adults at room temperatures in NDQCL

Time (month)	[a]Content%(w/w)		Drug rel % 30 min[b]		Degradation products	
	Batch No. 04J06	Batch No. 04J11	Batch No. 04J06	Batch No. 04J11	Batch No. 04J06	Batch No. 04J11
Zero	99.73±0.70	101.90±0.90	76.70±1.7	70.70±1.5	Not detected	
3 months	99.00±0.40	100.4±0.33	70.00±2.2	70.00±3.2	detected	
6 months	98.60±0.50	100.0±0.80	69.30±0.91	68.30±1.89	detected	
9 months	98.50±0.33	99.8±0.43	67.10±1.3	66.00±2.63	detected	
12 months	97.30±0.80	97.9±0.77	64.90±2.23	63.10±0.93	detected	
18 months	96.70±0.33	97.00±0.65	62.04±0.88	61.04±1.78	detected	
24 months	95.09±0.41	96.00±0.70	59.30±2.10	57.170±3.10	detected	

IP requirement:90-110 of amount stated on label(n=3);[b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement:<1.0%)
IP requirement for dissolution test >60%

Table No. (20): Results of analysis of Ariplus tablets for children at room temperature in NDQCL

Time (month)	[a]Content%(w/w)		Drug rel % 30 min[b].		Degradation products	
	Batch No. 04J22	Batch No. 04k04	Batch No. 04J22	Batch No. 04k04	Batch No. 04J22	Batch No. 04k04
Zero	102.00±0.30	101.50±0.50	77.66±1.9	70.32±3.2	Not detected	
3 months	100.10±0.41	100.20±0.66	59.78±3.10	57.00±3.50	detected	
6 months	100.40±0.33	99.40±0.43	50.90±0.99	52.40±1.20	detected	
9 months	99.10±0.77	99.10±0.67	48.30±3.5	49.83±2.5	detected	
12 months	98.30±0,40	98.30±0.70	46.00±3.1	46.90±1.9	detected	
18 months	97.20±0.60	98.20±0.50	45.90±1.60	45.00±1.60	detected	
24 months	9.90±0.55	97.80±0.45	43.68±1.12	42.99±2.62	detected	

IP requirement:90-110 of amount stated on label(n=3);[b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement <1.0%)
IP requirement for dissolution test >60%

Table No. (21): Results of analysis of Artemal tablets for children at room temperature in NDQCL

Time (month)	[a]Content%(w/w)		Drug rel % 30 min[b].		Degradation products	
	Batch No. E1041	Batch No. E1025	Batch No. E1041	Batch No. E1025	Batch No. E1041	Batch No. E1025
Zero	99.50±0.40	100.99±0.50	90.20±1.2	93± 1.90	Not detected	
3 months	99.00±0.20	100.00±0.60	88.90±1.13	91.60±2.00	detected	
6 months	99.10±0.101	99.77±0.31	88.00±2.2	90.00±1.80	detected	
9 months	98.30±0.30	99.00±0.30	87.40±0.90	88.90±2.30	detected	
12 months	96.90±0.45	98.90±0.75	87.00±2.1	87.90±3.10	detected	
18 months	96.00±0.33	97.00±0.63	86.90±1.67	86.00±1.97	detected	
24 months	95.10±0.78	95.90±0.33	84.30±0.89	85.93±0.99	detected	
36 months	93.99±0.90	95.22±0.49	81.60±2.10	84.60±3.10	detected	

IP requirement:90-110 of amount stated on label(n=3);[b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement<1.0%)
IP requirement for dissolution test >60%

Table No. (22): Results of analysis of Artemal tablets for adults at room temperature in NDQCL

Time (month)	[a]Content%(w/w)		Drug rel % 30 min[b].		Degradation products	
	Batch No. F0278	Batch No. F0622	Batch No. F0278	Batch No. F0622	Batch No. F0278	Batch No. F0622
Zero	101.69±0.34	100.00±0.34	86.95±2.2	95.95±1.92	Not detected	
3 months	100.90±0.30	99.90±0.80	85.00±1.99	94.00±0.98	detected	
6 months	100±0.44	98.0±0.74	82.10±0.88	92.10±0.88	detected	
9 months	99.60±0.35	98.10±0.66	85.20±2.80	90.20±2.80	detected	
12 months	98.13±0.88	96.10±0.48	84.00±1.50	90.00±1.50	detected	
18 months	97.20±0.65	95.20±0.35	80.90±2.60	87.00±3.60	detected	
24 months	95.10±0.42	94.30±0.40	76.10±1.14	85.00±1.44	detected	
36 months	94.22±0.50	92.92±0.60	73.56±1.90	82.00±1.50	detected	

IP requirement:90-110 of amount stated on label(n=3);[b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
IP requirement for dissolution test >60%

Table No. (23): Results of analysis of ASP tablets for children at room temperature in NDQCL

Time (month)	[a]Content%(w/w)		Drug rel % 30 min[b].		Degradation products	
	Batch No. 060806	Batch No. 060610	Batch No. 060806	Batch No. 060610	Batch No. 060806	Batch No. 060610
Zero	99.16±0.32	99.16±0.60	66.63±1.20	70.13±1.9	Not detected	
3 months	98.10±0.34	98.10±0.40	66.10±0.99	68.20±3.13	detected	
6 months	98.06±0.50	98.06±0.55	64.90±2.10	65.50±2.19	detected	
9 months	97.70±0.60	97.70±0.8	63.00±1.40	64.20±2.50	detected	
12 months	97.00±0.80	97.00±0.40	61.46±2.20	62.16±3.10	detected	
18 months	96.18±0.76	96.18±0.36	61.05±0.97	61.95±1.87	detected	
24 months	95.80±0.44	95.80±0.43	60.10±2.00	61.00±4.90	detected	

IP requirement:90-110 of amount stated on label(n=3);[b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
IP requirement for dissolution test >60%

Table No. (24): Results of analysis of ASP tablets for adults at room temperature in NDQCL

Time (month)	[a]Content%(w/w)		Drug rel % 30 min[b].		Degradation products	
	Batch No. 060624	Batch No. 0606523	Batch No. 060624	Batch No. 0606523	Batch No. 060624	Batch No. 0606523
Zero	99.60±0.39	100.00±0.70	77.82±1.90	81.82±0..99	Not detected	
3 months	99.10±0.40	99.90±0.33	77.00±2.10	77.00±2.60	detected	
6 months	98.00±0.555	98.80±0.61	76.10±2.30	76.10±3.30	detected	
9 months	97.30±0.64	98.28±0.74	74.80±1.70	73.80±0.99	detected	
12 months	97.10±0.34	97.10±0.34	72.50±0.99	70.50±2.1	detected	
18 months	96.00±0.77	96.00±0.77	68.80±1.10	68.80±1.88	detected	
24 months	94.80±0.63	94.90±0.63	65.92±3.10	63.92±4.10	detected	

IP requirement:90-110 of amount stated on label(n=3);[b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement:<1.0%)
IP requirement for dissolution test >60%

Table No. (25): Results of analysis of Artecosp tablets for children at room temperature in NDQCL

Time (month)	[a]Content%(w/w)		Drug rel % 30 min[b].		Degradation products	
	Batch No. 051020	Batch No. 051018	Batch No. 051020	Batch No. 051018	Batch No. 051020	Batch No. 051018
Zero	100.30±0.40	102.00±0.99	99.68±2.1	97.58±3.10	Not detected	
3 months	100.00±0.20	101.60±0.33	97.00±1.8	96.00±2.60	detected	
6 months	99.50±0.70	100.50±0.45	96.16±3.2	95.11±4.16	detected	
9 months	98.70±0.40	100.90±0.60	96.40±4.1	94.10±2.19	detected	
12 months	98.00±0.33	100.22±0.86	95.05±3.3	93.95±2.11	detected	
18 months	97.90±0.35	99.70±0.80	95.10±1-7	91.10±1.74	detected	
24 months	97.90±0.71	99.00±0.50	93.00±2.3	90.00±2.30	detected	

IP requirement:90-110 of amount stated on label(n=3);[b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement:<1.0%)
IP requirement for dissolution test >60%

Table No. (26): Results of analysis of of Artecosp tablets for adults at room temperature in NDQCL

Time (month)	[a]Content%(w/w)		Drug rel % 30 min[b]		Degradation products	
	Batch No. 051106	Batch No. 051021	Batch No. 051106	Batch No. 051021	Batch No. 051106	Batch No. 051021
Zero	100.20±0.40	105.20±0.77	97.46±2.3	100.00±3.40	Not detected	
3 months	99.90±0.54	105.00±0.34	97.00±2.20	99..00±3.20	detected	
6 months	100.00.33	103.99±.56	95.70±1.20	99.17±2.40	detected	
9 months	98.50±0.61	102.30±0.50	96.40±0.90	99.00±1.90	detected	
12 months	97.90±0.32	100..90±0.60	96.10±1.70	97.90±4.00	detected	
18 months	97.00±0.53	100.00±0.26	95.00±2.10	96.60±.3.20	detected	
24 months	96.00±0.42	98.80±0.88	93.40±0.99	95.40±0.60	detected	

IP requirement:90-110 of amount stated on label(n=3);[b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement:<1.0%)
IP requirement for dissolution test >60%

Table No. (31): Results of post -marketing surveillance of artesunate tablets (AS+SP) (Khartoum round one)

Product	Batch No	Supplier	H.F.	AC	[a]Content% (w/w)	D.T(min.[d])	Drug rel % 30 min[b].
Artesumine for Adult	040901	Private Company	Other	Working	103.97±0.44	9 min [with disc]	98.59 ±1.2
	041201	Private Company	Community pharmacy	Not Working	99.62 ±0.43	8 min [with disc]	95.45± 0.99
	040901	Private Company	Public pharmacy	Not Working	97.93 ±0.5	7 min [with disc]	95.96 ±2.1
Artesumine for Children	040801	Private Company	Community pharmacy	Not Working	100.62 ±0.7	More than 15 min [with disc] , 9 min [without disc]	95.17 ±2.3
	040801	Private Company	Public pharmacy	Not Working	99.96 ±0.43	More than 15 min [with disc], 9 min [without disc]	94.71 ±1.1
Ariplus for Adult	04J06	CMS	Other	Not Working	96.23 ±0.33	3 min [with disc]	66.09 ±0.98
	04J11	CMS	Public pharmacy	Not Working	99.71 ±0.67	6 min [with disc]	59.54±3.1
	04J29	CMS	Community pharmacy	Not Working	100.5 ±0.77	4 min [with disc]	62.39 ±2.3
	04106	Private Company	Hospital	Working	97.37 ±0.45	1:15 min	67.47± 2.2
Ariplus for Children	04K05	CMS	Other	Working	107.11±0.35	5 min [with disc]	47.96 ±±3.5
	04J22	CMS	Public pharmacy	Not Working	100.89 ±0.47	5 min [with disc]	50.29 ±2.2
	04J22	CMS	Community pharmacy	Working	100.33 ±0.66	6 min [with disc]	50.59± 1.4
	02L16	Private Company	Community pharmacy	Working	97.00±0.34	3:2 min	80.87±4.1

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement<1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (32): Results of post -marketing surveillance of artesunate tablets(AS+SP) (Elgadarif round one)

Product	Batch No	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
Artesumine for Adult	040901	Private Company	Community pharmacy	Not Working	103.41±0.33	9 min	95.55±1.5
	040901	Private Company	Public pharmacy	Working	100.77±0.43	More than 15min [with disc], 9 min [without disc]	98.81±2,3
Artesumine for Children.	040801	Private Company	Community pharmacy	Not Working	98.92±0.54	More than 15min [with disc], 9 min [without disc]	96.90± 1.2
	040901	Private Company	Public pharmacy	Working	103.17±0.77	More than 15min [with disc], 9:45 min [without disc]	97.07±0.99
Ariplus for Adult	04J06	CMS	Hospital	Working	99.98±0.46	3 min	53.18±1.9
	04J29	CMS	Other	Working	101.12±0.66	2:35 min	56.78±3-1
	04J11	CMS	Other	Not Working	98.84±0.44	3:45 min	56.09±3.3
	04J27	CMS	Public pharmacy	Working	98.02±0.46	3:40 min	54.64±2.3
	04J12	CMS	Community pharmacy	Working	98.82±0.71	More than 15min [with disc], 3:30 min [without disc]	57.01±1.5
Ariplus for Children.	04J22	CMS	Hospital	Working	100.02±0.5	4:45 min	41.66±0.99
	04J22	CMS	Other	Working	101.61±0.6	5 min	41.0±0.98
	04J22	CMS	Other	Not Working	101.3±80.34	5:40 min	48.75±3.1
	04J22	CMS	Public pharmacy	Working	99.89±0.4	5 min	42.02±0.89
	04J22	CMS	Community pharmacy	Not Working	100.25±0.6	6 min	39.91±2.4

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (33): Results of post -marketing surveillance of artesunate tablets (AS+SP) (Atbara round one)

Product	Batch. No	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
Artesumine for Adult	041201	Private Company	Community pharmacy	Working	97.51 ±0.3	8 min [with disc]	95.50±1.2
	041201	Private Company	Community pharmacy	Working	96.91± 0.6	8 min [with disc]	95.50± 0.90
	041201	Private Company	Public pharmacy	Working	93.42± 0.4	8 min [with disc]	92.10 ±1.6
Artesumine for Children	040901	Private Company	Community pharmacy	Working	99.48 ±0.8	More than 15min[with disc], 8 min [without disc]	98.2±3.1
Ariplus for Adult	04J27	CMS	Community pharmacy	Working	97.23 ±0.44	5 min [with disc]	56.47± 2.2
	04J29	CMS	Public pharmacy	Not Working	93.11± 0.36	3 min [with disc]	62.08 ±1.8
Ariplus for Children	04J22	CMS	Community pharmacy	Working	98.58 ±0.33	5 min [with disc]	50.11 ±1.9
	04J22	CMS	Other	Not Working	91.49 ±0.4	4 min [with disc]	45.35± 0.88
	04J22	CMS	Public pharmacy	Not Working	100.09 ±0.7	6 min [with disc]	47.76± 0.97

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (34): Results of post -marketing surveillance of artesunate tablets (AS+SP) (Elobied round one)

Product	Batch. No	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
Artesumine for Adult	040901	Private Company	Hospital	Not Working	100.63±0.44	More than 15min [with disc], 10 min [without disc]	96.79±3.2
Ariplus for Adult	04J11	CMS	Hospital	Not Working	98.33±0.5	4 min	57.04±1.9
	04J13	CMS	Community pharmacy	Working	99.17±0.6	5 min	58.21±1.98
Ariplus for Children	04J22	CMS	Hospital	Not Working	97.72±0.35	5 min	46.03±0.99
	04J22	CMS	Community pharmacy	Not Working	100.0±0.77	4:40 min	40.03±1.4
	04K04	CMS	Public pharmacy	Working	100.50±0.67	5 min	49.29±4.1

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement<1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (35): Results of post -marketing surveillance of artesunate tablets (AS+SP) (Khartoum round two)

Product	Batch No.	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
Artesumine for Adult	041201	Private Company	Hospital	Working	99.68±0.33	After 15 min 4 tabs remained [with disc] Dis after 9:4 min [without disc]	96.00±1.1
	041201	Private Company	Community pharmacy	Working	98.42±0.4	After 15 min one tab remained [with disc] Dis after 9:45 min [without disc]	96.51±1.2
	040901	Private Company	Community pharmacy	Working	101.00±0.6	After 15 min one tab remained [with disc] Dis after 8:50 min [without disc]	97.75±2.3
	041201	Private Company	Public pharmacy	Working	100.3±0.5	After 15 min one tab remained [with disc] Dis after 9:50 min [without disc]	98.32±0.9
Ariplus for Adult	05C29	CMS	Community pharmacy	Working	98.43±0.3	3 min [with disc]	61.49±2.4
	04J29	Private Company	Public pharmacy	Working	100.95±0.9	2 min [with disc]	64.89±1.1
	05C23	CMS	Community pharmacy	Working	96.82±0.66	3:17 min [with disc]	69.92±1.1
	05C23	CMS	Public pharmacy	Working	98.44±0.4	3:19 min [with disc]	60.88±2.5
	05001	CMS	Community pharmacy	Working	97.2±0.8	3:8 min [with disc]	52.84±1.3
	05005	CMS	Hospital	Working	98.5±0.4	4 min [with disc]	55.71±4.1
Ariplus for Children	04K04	Private Company	Community pharmacy	Working	98.2±0.43	4:30 min [with disc]	45.68±2.5
	04J22	CMS	Community pharmacy	Working	100.09±0.4	4:20 min [with disc]	43.79±2.3
	04106	Private Company	Community pharmacy	Working	93.16±.06	2:35 min [with disc]	81.02±1.4
	04J22	Private Company	Public pharmacy	Working	98.17±0.5	3:35 min [with disc]	45.08±0.9
Artemal for Adult	E1033	Private Company	Hospital	Working	98.89±0.7	32 Sec [with disc]	80.38±3.1
	F0278	Private Company	Public pharmacy	Not Working	96.18±0.5	35 Sec [with disc]	84.41±2.1
	E1027	Private Company	Community pharmacy	Working	95.7±0.44	40 Sec [with disc]	86.21±3.1
Artemal for Child	E1043	Private Company	Hospital	Working	95.01±0.50	32 Sec [with disc]	89..90±1.5
	E1043	Private Company	Community pharmacy	Working	96.00±0.6	50 Sec [with disc]	89.97±2.2
	E1041	Private Company	Public pharmacy	Working	94.64±0.44	45 Sec [with disc]	90.83±1.9

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (36): Results of post -marketing surveillance of artesunate tablets(AS+SP)(Elgadarif round two)

Product	Batch No.	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
Artesumine for Adult	050610	Private Company	Community pharmacy	Working	98.54±0.33	7:30 min [with disc]	96.66±2.1
	050610	Private Company	Community pharmacy	Working	100.74±0.5	7:43 min [with disc]	94.18±1.3
Artesumine for Children	050608	Private Company	Community pharmacy	Not Working	107.32±0.6	10 min [with disc]	96.65±2.1
	050608	Private Company	Hospital	Not Working	99.60±0.43	After 15 min 2 tabs remained [with disc] Dis after 9 min [without disc]	95.40±3.1
	050608	Private Company	Other	Not Working	103.74±0.8	After 15 min one tab remained [with disc] Dis after 9:10 min [without disc]	101.5±3.2
	041101	Private Company	Other	Not Working	103.13±0.4	14 min [with disc]	95.63±1.1
	041101	Private Company	Public pharmacy	Working	100.96±0.4	After 15 min 2 tab remained [with disc] Dis after 10:30 min [without disc]	94.15±1.4
	050608	Private Company	Community pharmacy	Working	104.43±0.8	one tab remained [with disc] Dis after 9min [without disc]	95.40±0.9
	050608	Private Company	Drug store	Working	103.57±0.6	2 tabs remained After 15 min [with disc] Dis after 8:45 min [without disc]	99.98±0.8
Ariplus for Adult	04J29	Private Company	Community pharmacy	Working	95.81±.0.45	1:45 min [with disc]	71.14±1.1
	04J12	CMS	Hospital	Not Working	99.74±0.6	2:19 min [with disc]	59.69±±1.4
	05C23	CMS	Other	Not Working	95.49±0.4	2:55 min [with disc]	62.56±2.1
	F0618	CMS	Public pharmacy	Working	91.49±0.6	3:15 min [with disc]	53.71±0.8
Ariplus for Children	04J22	Private Company	Community pharmacy	Working	93.04±0.8	2:00 min [with disc]	45.53±1.5
Artemal for Adult	F0622	Private Company	Community pharmacy	Working	96.48±0.4	52 Sec [with disc]	94.25±1.7
	F0618	CMS	Public pharmacy	Working	101.78±0.5	49 Sec [with disc]	89.27±0.8
	050610	Private Company	Community pharmacy	Working	98.25±0.7	After 15 min one tab remained [with disc] Dis after 9:48 min [without disc]	95.47±2.1
Artemal for Children	E1045	Private Company	Community pharmacy	Working	101.53±0.3	37 Sec [with disc]	93.06±1.1
	E1039	Private Company	Public pharmacy	Working	100.67±0.7	33 Sec [with disc]	93.81±0.7

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (37): Results of post- marketing- surveillance of artesunate tablets (AS+SP) (Atbara round two)

Product	Batch No.	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
Artesumine for Adult	041201	Private Company	Community pharmacy	Working	99.20 ±0.6	After 15 min 5 tab remained [with disc] Dis after8:40 min [without disc]	75.56±1.1
Artesumine for Children	040901	Private Company	Community pharmacy	Working	102.32±0.4	After 15 min 3 tab remained [with disc] Dis after 8:20 min [without disc]	100±1.4
Ariplus for Adult	05011	CMS	Hospital	Working	97.80±0.33	4 min [with disc]	42.33±2.4
	05C29	CMS	Community pharmacy	Working	96.81±0.8	4:20 min [with disc]	48.06±3.1
	05001	CMS	Community pharmacy	Not Working	102.27±0.6	4 min [with disc]	47.13±4.1
	05005	CMS	Public pharmacy	Working	98.21±0.5	3:45 min [with disc]	52.33±2.2
	05C23	CMS	Drug Store	Working	99.72±0.4	3:30 min [with disc]	54.73±0.9
Ariplus for Children	040901	Private Company	Hospital	Working	100.79±0.23	After 15 min 2 tab remained [with disc] Dis. after 9 min [without disc]	94.59±0.8
	04K04	CMS	Other	Working	97.27±0.6	4 min [with disc]	44.82±1.3
	04K05	Private Company	Community pharmacy	Working	97.76±0.6	4:25 min [with disc]	41.72±2.1
	04K04	CMS	Public pharmacy	Working	101.19±0.7	4:45 min [with disc]	45.73±1.5
Artemal for Adult	E1029	Private Company	Community pharmacy	Working	98.58±0.5	30 Sec [with disc]	77.57±2.5
	E1031	Private Company	Public pharmacy	Not Working	98.23±0.4	30 Sec [with disc]	96.50±2.3
Artemal for Children	E1041	Private Company	Drug Store	Working	96.75±0.33	1:15 min [with disc]	93.00±1.9

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (38): Results of post -marketing surveillance of artesunate tablets (AS+SP) (Elobied round two)

Product	Batch No.	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	D rug rel % 30 min[b].
Artesumine for Adult	041201	Private Company	Community pharmacy	Not Working	96.42±0.5	1 tab remain After 15 min [with disc] Dis after 10:15 min [without disc]	96.07±1.3
	041201	Private Company	Other	Not Working	97.95±0.7	1 tab remain After 15 min [with disc] Dis after 9:35 min [without disc]	96.58±2.2
	041201	Private Company	Hospital	Working	99.33±0.8	1 tab remain After 15 min [with disc] Dis after 9:45 min [without disc]	98.71±2.3
Artesumine for Children	050608	Private Company	Community pharmacy	Not Working	95..55±0.33	1 tab remain After 15 min [with disc] Dis after 8:45 min [without disc]	93.55±1.4
	040801	Private Company	Hospital	Not Working	98.53±0.5	1 tab remain After 15 min [with disc] Dis after 8:45 min [without disc]	96.51±1.5
	050608	Private Company	Hospital	Not Working	98.35±0.7	1 tab remain After 15 min [with disc] Dis after 8:30 min [without disc]	98.31±3.1
	041101	Private Company	Public pharmacy	Not Working	97.73±0.4	1 tab remain After 15 min [with disc] Dis after 10 min [without disc]	96.72±2.1
Artemal for Adult	041201	Private Company	Hospital	Not Working	95.62±0.6	11 min [with disc]	92.77±0.9
	E1033	Private Company	Hospital	Not Working	93.82±0.3	32 Sec [with disc]	83.61±2.2
	E1033	Private Company	Community pharmacy	Not Working	90.68±0.7	33 Sec [with disc]	84.29±3.2
Artemal for Children	E1039	Private Company	Public pharmacy	Not Working	94.98±0.8	50 Sec [with disc]	89.1±1.7
	E1039	Private Company	Community pharmacy	Not Working	94.71±0.6	44 Sec [with disc]	88.39±1`.9
Ariplus for Children	04J22	Private Company	Other	Not Working	95.72±0.4	3:30 min [with disc]	46.32±3.1
Ariplus for Adult	05005	CMS	Public pharmacy	Working	96.16±0.8	2:25 min [with disc]	52.79±1.1

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (39): Results of post- marketing surveillance of artesunate tablets (AS+SP) (Khartoum round three)

Product	Batch No.	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
Combisunate for Adult	P0555C	CMS	Community pharmacy	Working	94.27±0.5	18 Sec [with disc]	59.32±1.2
	P0595C	CMS	Hospital	Working	89.40±0.6	12 Sec min [with disc]	54.71±2.3
	P0585C	CMS	Public pharmacy	Working	87.46±0.7	10 Sec [with disc]	52.90±2.5
Artemal for Children	E1039	Private Company	Public pharmacy	Working	97..33±0.5	48 Sec [with disc]	90.91±1.9
	E1043	Private Company	Community pharmacy	Not Working	96.68±0.4	3 min [with disc]	90.435±2.7
	F1025	CMS	Public pharmacy	Working	98.73±0.33	1:50 Sec [with disc]	92.91±0.9
	F1025	Private Company	Public pharmacy	Working	94..92±0.4	2 min [with disc]	91.03±3.1
Artemal for Adult	F1017	Private Company	Community pharmacy	Working	96..30±0.5	55 Sec [with disc]	91.43±2.4
	F1021	CMS	Public pharmacy	Working	97..97±0.6	1:52 min [with disc]	83..84±1.7
Artesumine for Adult	051115	Private Company	Community pharmacy	Working	102.19±0.4	7 min [with disc]	94.025±2.1
	050610	Private Company	Public pharmacy	Working	99..36±0.34	6:9 min [with disc]	82.51±4.1
Artesumine for Children	051114	Private Company	Public pharmacy	Working	105.63±0.6	9 min [with disc]	95.13±2.3
	051114	Private Company	Community pharmacy	Working	98..85±0.8	7:33 min [with disc]	96.18±0.9

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement<1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (40): Results of post- marketing surveillance of artesunate tablets (AS+SP) (Elgadarif round three)

Product	Batch No.	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
Artesumine for Children	050909	Private Company	Public pharmacy	Working	104.21±0.4	13 min [with disc]	91.46±1.1
	050608	Private Company	Other	Not Working	98.41±0.7	10:12 min [with disc]	100.63±3.1
	050909	Private Company	Community pharmacy	Working	102.62±0.4	9:39 min [with disc]	90.48±1.5
Artesumine for Adult	051115	Private Company	Community pharmacy	Working	108.06±0.7	11 min [with disc]	94.27±1.8
	050610	Private Company	Public pharmacy	Working	101.47±0.4	10 min [with disc]	96.23±1.7
Artemal for Children	F1025	Private Company	Community pharmacy	Not Working	101.18±0.3	2:10 min [with disc]	85.16±2.1
	F1025	CMS	Public pharmacy	Working	104.66±0.4	2 min [with disc]	94.57±2.2
Combisunate for Adult	P0555C	CMS	Public pharmacy	Working	94.11±0.9	30 Sec [with disc]	49.48±1.5
	P0575C	CMS	Other	Not Working	90.55±0.8	48 Sec [with disc]	53.70±1.4
	P0575C	CMS	Community pharmacy	Not Working	89.92±0.4	23 Sec [with disc]	53.53±2.1
	P0585C	CMS	Community pharmacy	Not Working	91.40±0.6	20 Sec [with disc]	55.23±1.1
Artescope for Adult	051111	Other	Other	Not Working	100.87±0.4	7:27 min [with disc]	92.19±0.9
	051111	Other	Drug Store	Not Working	105.21±0.8	15 min [with disc]	90.27±0.9
	051106	Other	Other	Not Working	99.69±0.4	8:11 min [with disc]	90.84±2.2
	051106	Other	Hospital	Working	100.04±0.3	7:23 min [with disc]	89.78±3.2
Artescope for Children	051018	Other	Other	Not Working	103.12±0.6	8 min [with disc]	100.03±1.4
	051013	Other	Other	Not Working	99.67±0.4	13 min [with disc]	94.90±1.3
	051020	Other	Hospital	Working	100.00±0.7	14 min [with disc]	99.00±2.3
	051018	Other	Drug Store	Not Working	105.20±0.8	14:2 min [with disc]	97.25±2.1

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (41): Results of post- marketing surveillance of artesunate tablets (AS+SP) (Atbara round three)

Product	Batch No.	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
Artemal for Adult	F1019	CMS	Other	Not Working	101.6±0.5	4 Sec [with disc]	94.38±1.1
	F1019	Private Company	Public pharmacy	Not Working	98.98±0,3	1.5 min [with disc]	93.61±3.2
Artemal for Children	F1023	CMS	Other	Not Working	107.04±0.7	52 Sec [with disc]	100.18±2.2
	F1023	Private Company	Community pharmacy	Working	102.59±0.6	1.5 min [with disc]	96.19±3.1
	F1025	Private Company	Public pharmacy	Not Working	103.08±0.5	50 Sec [with disc]	91.01±1.4
Combisunate for Adult	P0595C	CMS	Public pharmacy	Not Working	86.19±0.3	36 Sec [with disc]	53.14±0.9
	*P0595C	CMS	Other	Not Working	92.21±0.6	40 Sec [with disc]	47.82±1.8
	P0585C	CMS	Community pharmacy	Working	93.21±0.7	42 Sec [with disc]	49.52±0.9
	P0585C	CMS	Hospital	Working	93.21±0.4	40 Sec [with disc]	51.29±2.2
Artesumine for Children	050909	Private Company	Public pharmacy	Working	94.84±0.6	13 min [with disc]	94.61±4.1
	050704	Private Company	Public pharmacy	Not Working	100.89±0.8	12 min [with disc]	95.75±2.4
	051114	Private Company	Community pharmacy	Not Working	104.24±0.3	7 min [with disc]	103.61±3.3
Artesumine for Adult	051209	Private Company	Community pharmacy	Not Working	101.89±0.6	12 min [with disc]	89.59±2.3
	051115	Private Company	Public pharmacy	Working	102.38±0.4	11 min [with disc]	98.38±3.2

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)

[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%. *=not comply physical appearance

Table No. (42): Results of post- marketing surveillance of artesunate tablets (AS+SP) (Elobied round three)

Product	Batch No.	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
Artescope for Adult	051106	Other	Drug Store	Not Working	99.60±0.3	9 min [with disc]	90.74±1.0
	051110	Other	Drug Store	Working	102.14±0.4	11:20 min [with disc]	92.04±2.1
	051021	Other	Hospital	Not Working	100.50±0.6	10 min [with disc]	94.11±2.2
	051021	Other	Other	Not Working	107.80±0.7	After 15 min [with disc] Dis after 9:40 min [without disc]	101.33±1.3
	051111	Other	Other	Not Working	100.50±0.7	9 min [with disc]	93.77±1.4
Artescope for Children	051018	Other	Hospital	Not Working	101.70±0.3	After 15 min [with disc] 9:52 min [without disc]	100.8±`0.3
	051018	Other	Drug Store	Not Working	102.20±0.4	9:13 min [with disc]	95.42± 2.3
	051009	Other	Drug Store	Working	105.23±0.9	After 15 min [with disc] Dis after 10:20 min [without disc]	96.80±1.6
	051018	Other	Other	Not Working	104.1±0.5	10 min [with disc]	94.54±3.1
	051013	Other	Other	Not Working	105.21±0.6	After 15 min [with disc] Dis after 11 min [without disc]	101.51±1.1
Artemal for Adult	F1021	Private Company	Community pharmacy	Working	101.32±0.4	2 min [with disc]	96.45±0.9
Artemal for Children	G0228	Private Company	Community pharmacy	Working	97.03±0.3	1:52 min [with disc]	91.68±2.2
Artesumine for Adult	051209	Private Company	Community pharmacy	Not Working	98.00±0.7	10 min [with disc]	82.43±3.1
	051209	Private Company	Community pharmacy	Working	102.14±0.3	10:35 min [with disc]	89.97±4.1
Artesumine for Children	051114	Private Company	Community pharmacy	Not Working	101.10±0.8	13:55 min [with disc]	87.61±1.1
	051114	Private Company	Community pharmacy	Working	104.18±0.6	7 min [with disc]	97.11±2.2

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (43): Results of post -marketing surveillance of artesunate tablets(AS+SP) (Khartoum round four)

Product	Batch No.	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
Artesumine for Adult	LS 060602	Private company	Public pharmacy	Working	103.47±0.3	9 min with disc	85.68±1.1
	LS 060602	Private company	Hospital	Working	109.68±0.4	8:20 min with disc	90.84±2.1
	LS 060301	Private company	Community pharmacy	Not working	101.14±0.8	12 Min with disc	83..93±3.1
Artesumine for Children	G 0228	Private company	Public pharmacy	Working	104.61±0.4	51 sec with disc	91.77±2.3
	051208	Private company	Hospital	Not working	101.69±0.6	14min with disc	91.76±3.3
	051114	Private company	Community pharmacy	Not working	105.26±0.4	After 15 min one tab remained with disc ,disc after 9:1 min without disc	92.02±1.8
Artemal for Adult	F 1017	Private company	Community pharmacy	Not working	101.12±0.33	4 sec with disc	91.03±3.2
	F 1017	Private company	Other	Not working	95.65±o.5	10 sec with disc	79.40±2.1
Artemal for Children	F 1025	Private company	Community pharmacy	Working	109.5±0.8	40 sec with disc	94.61±1.1
ASP for Adult	060624	Private company	Community pharmacy	Not working	96.22±0.5	7 min with disc	79.74±4.1
	060624	Private company	Drug store	Not working	98.99±0.3	8 min with disc	80.00±1.9
	060523	Private company	Other	Not working	98.08±0.5	10 min with disc	65.45±2.5
	060528	Private company	Other	Not working	94.00±0.7	8 min with disc	61.64±2.2
ASP for Children	060806	Private company	Drug store	Not working	97.65±0.3	13 min with disc	66.82±2.3
	060610	Private company	Community pharmacy	Not working	99.46±9.5	15 min with disc ,	79.08±1.5

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement<1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (44): Results of post- marketing surveillance of artesunate tablets (AS+SP) (Atbara round four)

Product	Batch No.	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
ASP for Children	060806	CMS	Other	Not working	99.83±0.6	12 min with disc	70.87±1.1
	060610	CMS	Drug store	working	96.69±0.4	13 min with disc	77.98±1.3
	060517	CMS	Drug store	Not working	99.96±0.5	14 min with disc	62.81±2.1
	061005	CMS	Other	Not working	96..36±0.8	15 min with disc	73.04±0.9
ASP for Adult	060619	CMS	Other	Not working	97.18±0.3	7 min with disc	75.99±2.2
	060101	CMS	Drug store	Not working	101.64±0.4	11 min with disc	70.49±4.1
	060615	CMS	Community pharmacy	Not working	95..27±0.3	8 min with disc	68.27±3.3
	060629	CMS	Drug store	Working	96.74±0.5	8 min with disc	68.11±1.3
Artemal for Adult	F 1021	CMS	Other	Not working	95.6o±0.6	4 sec with disc	82.83±2.3
	F 1019	CMS	Public pharmacy	Not working	98..36±0.3	6sec with disc	81.17±2.2
	F 1169	CMS	Community pharmacy	Not working	101.40±0.6	5 sec with disc	77.88±1.5
Artemal for Children	F 1023	CMS	Other	Not working	95.06±0.5	50 sec with disc	90.85±1.9
	F 1023	CMS	Hospital	Not working	100.34±0.7	45 sec with disc	93.93±4.2
	G 0226	CMS	Community pharmacy	Not working	95.16±0.4	50 sec with disc	90.95±2.2
Artesumine for Children	051114	Private company	Community pharmacy	Not working	97.77±0.8	After 15 min one tab remained with disc ,after 7 min without disc	80.43±3.4
Artesumine for Adult	051115	Private company	Other	Not working	96.19±0.3	8 min with disc	73.65±4.1
	051209	Private company	Community pharmacy	Not working	99.01±0.4	9 min with disc	90.0 ±2.3

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement<1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (45): Results of post -marketing surveillance of artesunate tablets(AS+SP) (Elobied round four)

Product	Batch No.	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
Artesumine for children	051208	Private company	Public pharmacy	Not working	100.27±0.3	8:20 min with disc	86.56±2.2
	051114	Private company	Community pharmacy	working	100.58±0.4	After 15 min one tab remained with disc ,after 7min without disc	95.45±2.1
	051114	Private company	Hospital	Not working	100.3±0.6	After 15 min one tab remained with disc ,after 10 min without disc	90.87±2.2
ASP for Adult	060528	Private company	Public pharmacy	Not working	96.34±0.7	8 min with disc	59.77±3.2
	060528	Private company	Community pharmacy	Not working	94.13±0.4	9 min with disc	59.61±4.1
Artesumine Adult	050610	Private company	Hospital	Not working	102.0±0.7	12 min with disc	84.75±1.1
	LS 060301	Private company	Community pharmacy	working	98.61±0.3	11 min with disc	94.99±2.1
Artemal for Children	G 0228	Private company	Community pharmacy	Not working	98.20±0.4	51 sec with disc	96.91±3.1
	00226	Private company	Public pharmacy	Not working	96.49±0.5	40 sec with disc	86.1±3.3
	F1023	CMS	Community pharmacy	Not working	97.03±0.7	44 sec with disc	88.6±3.4
Artecospe for Adult	051106	Other	Hospital	Not working	100.13±0.3	7 min with disc	86.66±1.4
	051021	Other	Other	Not working	97.83±0.6	10 min with disc	90.3±1.2
	051021	Other	Drug store	Working	100.33±0.4	8 min with disc	99.05±1.1
	051106	Other	Drug store	Not working	97.78±0.7	9 min with disc	90.0±70.9
Artecospe for Children	051013	Other	Hospital	Not working	97.42±0.4	8min with disc	95.05±2.4
	051013	Other	Drug store	Working	99.62±0.3	After 15 min one tab remained with disc ,after 7 min without disc	98.7±2.2
	051013	Other	Other	Not working	98.69±0.5	After 15 min one tab remained with disc ,after 10 min without disc	94.72±1.7
	05009	Other	Drug store	Not working	99.89±0.3	After 15 min one tab remain with disc ,after 9 min without disc	98.71±1.9

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (46): Results of post -marketing surveillance of artesunate tablets (AS+SP) (Khartoum round five)

Product	Batch No.	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
ASP for Adult	060625	CMS	Public pharmacy	working	97.22±0.4	10 min with disc	82.08± 2.7
	060621	Private company	Community pharmacy	working	94.44±0.7	12 min with disc	74.1 ±3.2
	060624	CMS	Drug store	working	95.09±0.5	12 min with disc	73.41± 1.3
ASP for Children	061006	CMS	Public pharmacy	working	93.69±0.3	12:45 min with disc	68.25 ±2.2
	060901	CMS	Community pharmacy	working	98.3±0.5	13 min with disc	87.32 ±1.9
	060610	Private company	Hospital	working	96.26±0.3	13 min with disc	84.07 ±1.7
	060806	Private company	Drug store	working	93.78±0.6	13 min with disc	67.58 ±1.5
Artesumine for Adult	LS061201	Private company	Public pharmacy	working	100.81±0.4	9 min with disc	89.82 ± 3.3
	LS061201	Private company	Community pharmacy	working	99.13±0.8	8:45 min with disc	93.29± 3.2
Artesumine for Children	051208	Private company	Public pharmacy	Not working	102.21±0.5	10 min with disc	88.70 ± 0.9
	051208	Private company	Community pharmacy	Not working	96.98±0.4	11 min with disc	93.45 ± 1.1
	041101	Private company	Drug store	working	101.57±0.3	9:30 min with disc	94.22 ±4.1
Artemal for Adult	G0220	CMS	Community pharmacy	working	95.1±0.4	2:20 min with disc	76.68 ±2.1
Artemal for Children	G0226	Private company	Community pharmacy	working	97.44±0.6	2:00 min with disc	82.08±2.1

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (47): Results of post- marketing surveillance of artesunate tablets (AS+SP) (Elgadarif round five)

Product	Batch No.	Supplier	H.F.	AC	[a]Content%(w/w)	D.T (min.[d])	Drug rel % 30 min[b].
Artescope for Adult	051021	Other	Hospital	Not working	99.64±0.4	13.00 min with disc	88.70±2.1
	051021	Other	Other	Not working	97.84±0.3	14.2 min with disc	85.52±1.3
	05102	Other	Hospital	working	98.00±0.6	9.23 min with disc	83.68±2.5
	051021	Other	Drug store	Not working	98.68±0.4	14.35 min with disc	84.60±2.2
Artescope for Children	051018	Other	Other	Not working	99.5±0.7	14:00 min with disc	97.61± 3.2
	051009	Other	Hospital	working	101.56±0.3	9:00 min with disc	94.71±3.1
	051013	Other	Drug store	Not working	98.56±0.4	8 min with disc	94.25± 4.1
	051013	Other	Other	Not working	101.18±0.3	7:45 min with disc	93.44 ±3.5
	051018	Other	Hospital	Not working	100.5±0.6	9:55 min with disc	99.35± 1.1
Artesumine for Adult	LS061201	Private company	Community pharmacy	working	98.64±0.9	11 min with disc	81.63 ±2.1
	LS061201	Private company	Community pharmacy	working	99.96±0.3	11:20 min with disc	86.67± 0.9
	050908	Private company	Public pharmacy	working	99.06±0.30.	9 min with disc	87.08 ±0.8
Artesumine for Children	LS060401	Private company	Community pharmacy	working	97.0±0.5	10 min with disc	95.5± 1.1
	LS060401	Private company	Community pharmacy	working	101.40.±0.6	10:1 min with disc	100.66± 0.7
	051208	Private company	Public pharmacy	working	100.8±0.3	8:33 min with disc	99.7± 0.6
Artemal for Adult	F1169	Private company	Community pharmacy	working	97.3±60.5	2 min with disc	69.6± 0.9
	G0220	Private company	Community pharmacy	working	98.5±0.8	3 min with disc	69.01± 4.2
Artemal for Children	G0228	Private company	Community pharmacy	working	93.99±-0.3	2:5 min with disc	75.32 ±1.1
ASP for Adult	060529	CMS	Drug store	Not working	98.05±0.6	13 min with disc	69.35± 1.2
	060529	CMS	Hospital	Not working	96.27±0.7	11:81 min with disc	68.62 ±2.2

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (48): Results of post -marketing surveillance of artesunate tablets (AS+SP) (Atbara round five)

Product	Batch No.	Supplier	H.F.	AC	[a]Content%(w/w)	D.T (min.[d])	Drug rel % 30 min[b].
Artescope for Adult	LS060903	Other	Drug store	Not working	100.10±0.7	14:00 min with disc	92.40 ±2.1
	LS060903	Other	Hospital	working	99.78±0.5	9:30 min with disc	94.82± 2.2
	LS060903	Other	Other	working	101.61±0.4	11:2 min with disc	91.27 ±1.6
Artescope for Children	LS060902	Other	Drug store	Not working	91.50±0.8	10:00 min with disc	80.08 ±1.8
	LS060902	Other	Hospital	working	102.57±0.3	8:00 min with disc	101.45±3.2
	LS060902	Other	Other	working	104.02±0.5	8:15 min with disc	93.24 ±3.1
ASP for Adult	060614	CMS	Drug store	working	98.39±0.6	7:45 min with disc	70.33 ±4.1
	060615	CMS	Community pharmacy	Not working	97.74±0.4	13 min with disc	74.62 ±1.1
	060621	CMS	Public pharmacy	working	97.19±0.4	9 min with disc	73.87 ±3.1
ASP for Children	060901	CMS	Public pharmacy	working	96.63±0.5	11 min with disc	82.87 ±2.2
	060901	CMS	Community pharmacy	Not working	94.01±0.3	11 min with disc	82.89± 2.3
	061005	CMS	Drug store	working	94.83±0.3	10 min with disc	75.83± 2.2
Artesumine for Adult	LS060902	Private company	Public pharmacy	working	102.62±0.7	11 min with disc	91.34 ±0.9
Artesumine Children	051208	Private company	Public pharmacy	working	99.59±0.5	9 min with disc	96.27 ±1.9
Artemal for Children	F023	Private company	Other	working	98.38±0.5	2 min with disc	91.08 ±2.8

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (49): Results of post- marketing surveillance of artesunate tablets (AS+SP) (Elobied round five)

Product	Batch No.	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
Artescope for Adult	051106	Other	Hospital	Not working	100.29±2.1	12:00 min with disc	94.82±0.3
	LS070205	Other	Other	Not working	97.59±0.9	10 min with disc	91.24±2.1
	LS070203	Other	Other	Not working	96.65±0.5	12:22 min with disc	95.09±1.5
	LS070203	Other	Drug store	Not working	96.29±0.6	13 min with disc	91.59±1.6
Artescope for Children	051013	Other	Hospital	Not working	97.06±0.3	11 min with disc	90.13±2.3
	051020	Other	Other	Not working	95.96±0.6	10:30 min with disc	96.11±1.5
	051018	Other	Other	Not working	96.72±0.2	13 min with disc	95.79±2.2
	LS070301	Other	Drug store	Not working	98.62±0.2	10 min with disc	91.66±3.3
Artesumine for Adult	LS061201	Private company	Community pharmacy	working	98.16±0.3	11 min with disc	93.31±1.8
	LS060301	Private company	Other	working	98.40±0.8	11min with disc	88.58±2.2
Artesumine for Children	051114	Private company	Other	working	105.81±0..9	9 min with disc	100.15±4.1
	051114	CMS	Hospital	working	98.16±0.2	10 min with disc	96.79±1.1
	LS060401	Private company	Community pharmacy	working	99.08±0.4	11 min with disc	96.13±2.2
Artemal for Adult	F1021	Private company	Community pharmacy	working	99.43±0.2	2:30 min with disc	81.78±4.1
Artemal for Children	G0228	Private company	Community pharmacy	Not working	92.9±0.3	3 min with disc	86.92±3.1
	G0228	CMS	Hospital	working	101.92±0.4	2 min with disc	81.14±1.1
ASP Adult	060624	CMS	Hospital	Not working	96.53±0.6	13:50 min with disc	79.56±1.2
	060615	CMS	Community pharmacy	working	93.23±0.7	13 min with disc	75.47±1.7
ASP for Children	061005	CMS	Hospital	Not working	97.9±0.8	14 min with disc	75.01±2.8
	060901	CMS	Community pharmacy	working	93.23±0.3	12 min with disc	86.25±1.1

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (50): Results of post -marketing surveillance of artesunate tablets (AS+SP) (Khartoum round six)

Product	Batch No.	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
ASP for Children	LS060902	Other	Other	Not working	101.23±0.5	11 min with disc	92.12±1.0
	061004	CMS	Public Pharmacy	working	100.55±0.3	11 min with disc	83.91±1.1
	061010	CMS	Hospital	working	94.81±0.4	10 min with disc	84.41±2.4
	061009	Private company	Public Pharmacy	working	97.46±0.7	13 min with disc	82.86±2.4
	061006	CMS	Community Pharmacy	working	94.29±0.6	11 min with disc	69.87±4.1
	060805	Private company	Drug Store	Not working	96.96±0.4	14 min with disc	67.75±2.3
ASP for Adult	060614	Private company	Other	working	98.93±0.3	11 min with disc	80.87±3.1
	061123	CMS	Public Pharmacy	working	100.35±0.8	7 min with disc	81.70±0.9
	061122	Private company	Hospital	working	95.00±0.5	9 min with disc	81.29±3.8
	061130	CMS	Community Pharmacy	working	96.60±0.3	7 min with disc	80.87±1.9
Artemal for Adult	F1169	Private company	Hospital	working	96.08±0.5	33 sec with disc	84.05±0.8
	G0220	Private company	Public Pharmacy	working	96.83±0.7	30 sec with disc	80.44±0.7
Artemal for Children	H0237	Private company	Public Pharmacy	working	100.12±0.6	50 sec with disc	84.13±2.1
Artesumine for children	L5060601	Private company	Public Pharmacy	working	98.10±0.3	8 min with disc	92.37±2.2
	051114	Private company	Community Pharmacy	working	94.69±0.5	9 min with disc	92.57±1.4
Artesumine for Adult	L5070401	Private company	Public Pharmacy	working	101.50±0.4	9 min with disc	91.66±1.3

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (51): Results of post -marketing surveillance of artesunate tablets (AS+SP) (Elgadarif round six)

Product	Batch No.	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
Artecosp for Children	LS070202	Other	Drug store	Not working	100.21±0.4	10 min without dsc	97.92±1.6
	051009	Other	Hospital	Not working	101.34±0.5	10 min without dsc	95.25±1.2
	L5070202	Other	Drug store	Not working	98.87±0.3	11 min without dsc	94.5±1.3
ASP for Children	061004	CMS	Public pharmacy	Not working	99.72±0.6	9 min with dsc	81.54±3.2
Artecosp for Adult	LS070205	Other	Hospital	Not working	103.56±0.4	13 min without dsc	101.24±2.0
	L5070203	Other	Drug store	Not working	99.32±0.3	14 min without dsc	92.03±3.7
ASP Adult	060614	CMS	Community pharmacy	working	60.3±0.59	7 min with dsc	67.27±0.9
	060626	CMS	Public pharmacy	working	94.56±0.49	7 min withdsc	76.00±1.1
Artemal for Children	F1023	Private company	Community pharmacy	working	97.42±0.3	44 sec with dsc	83.59±2.1
Artemal for Adult	G0383	Private company	Public pharmacy	Not working	93.60±0.6	50see with dsc	65.98±1.1
Artesumine for Adult	L5061201	Private company	Public pharmacy	Not working	100.60±0.4	11 min without dsc	90.83±0.9
	050610		Community pharmacy	working	99.44±0.8	9 min without dsc	93.15±3.2
Artesumine for Children	051208	Private company	Public pharmacy	working	102.46±0.9	40sec with dsc	100.1±3.3

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement<1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

94.56±0.59

Table No. (52): Results of post -marketing surveillance of artesunate tablets (AS+SP) (Atbara round six)

Product	Batch No.	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
Artecosp for Children	LS060902	Other	Drug store	Not working	100.74±0.7	10 min without disc	95.56±0.9
	LS070510	Other	Other	working	99.29±0.3	8 min without disc	99.0±2.2
	LS070510	Other	Hospital	Not working	100.96±0.3	9 min without disc	98.48±3.0
	051018	Other	Other	Not working	104.19±0.4	9 min without disc	103.06±2.2
ASP for Children	061006	CMS	Community pharmacy	working	96.70±0.5	10 min with disc	76.60±3.1
	061006	CMS	Public pharmacy	working	95.40±0.3	9 min with disc	78.92±4.1
	061009	CMS	Drug store	working	97.31±0.9	9 min with disc	85.20±3.5
Artecosp for Adult	LS060903	Other	Drug store	Not working	97.07±0.4	14 min without disc	91.9±30.9
	LS070511	Other	Other	working	103.02±0.6	10 min without disc	94.92±0.8
	LS070511	Other	Hospital	Not working	98.34±0.4	13 min without disc	89.62±3.2
	LS060903	Other	Other	Not working	103.22±0.5	13 min without disc	91.72±4.1
ASP for Adult	060620	CMS	Community pharmacy	working	103.06±0.3	10 min with disc	67.12±3.3
	060618	CMS	Public pharmacy	Not working	99.33±0.7	11 min with disc	69.60±2.2
	070501	CMS	Drug store	working	95.33±0.6	9 min with disc	78.65±2.3
Artemal for Children	G0226	Private company	Other	working	93.96±0.3	35 sec with disc	81.58±2.7
	G 0226	Private company	Public pharmacy	working	94.34±0.6	33 sec with disc	92.80±1.8
Artesumine for Children	LS060401	Private company	Public pharmacy	working	101.43±0.5	6 min without disc	99.38±1.9
Artesumine for Adult	LS070401	Private company	Public pharmacy	working	101.55±0.4	8 min without disc	93.61±2.0

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table No. (53): Results of post-marketing surveillance of artesunate tablets (AS+SP) (Elobied round six)

Product	Batch No.	Supplier	H.F.	AC	[a]Content% (w/w)	D.T (min.[d])	Drug rel % 30 min[b].
ASP for Children	070602	Private company	Public pharmacy	working	93.63±0.6	10 min with disc	84.73±3.3
	061020	Private company	Community pharmacy	working	95.01±0.9	10 min with disc	75.75±2.2
ASP for Adult	060814	Private company	Public pharmacy	working	97.97±0.8	10 min with disc	73.73±2.1
	070505	Private company	Community pharmacy	working	98.70±0.3	10 min with disc	76.64±3.2
Artemal for Children	G0228	Private company	Hospital	working	98.27±0.5	40sec with disc	82.59±1.1
Artesumine for Children	LS060601	Private company	Public pharmacy	working	100.20±0.4	7 min without disc	91.37±4.0
	LS060401	Private company	Community pharmacy	working	98.5±0.9	9 min without disc	91.34±3.0
	051114	Private company	Hospital	working	102.22±0.7	8 min without disc	95.59±3.2
Artecosp for Children	LS060902	Other	Hospital	Not working	96.94±0.6	9 min without disc	92.0±2.2
	LS060902	Other	Drug Store	Not working	95.35±0.5	8 min without disc	93.73±±3.7
	LS060902	Other	Other	Not working	98.27±0.8	8 min without disc	96.68±0.9
Artesumine for Adult	LS070401	Private company	Public pharmacy	Not working	100.22±0.4	13 min with disc	87.49±1.5
	LS061201	Private company	Hospital	working	98.02±0.3	11 min with disc	95.22±4.2
Artecosp for Adult	LS060903	Other	Drug Store	Not working	99.97±0.4	14 min without disc	98.8±2.2
	LS070302	Other	Other	Not working	99.97±0.6	13 min without disc	96.72±1.9

IP requirement:90-110 of amount stated on label(n=3); [b]n =6; all brands had satisfactory physical appearance and passed related substances test (IP requirement: <1.0%)
[d]n=6(IP requirement <15min). IP requirement for dissolution test >60%

Table: (54)Mean temperature and humidity (2005-2006-2007- 2008)
Station : Elobied

Month	Mean Temperature °C		Mean Relative Humidity%
	Max	Min	
January	29.8	14.8	25
February	35.5	16.1	18
March	36.8	20.5	13
April	35.6	23.0	26
May	37.0	25.2	40
June	37.8	24.1	52
July	34.0	23.2	64
August	32.2	22.0	74
September	33.3	21.7	73
October	36.0	22.6	42
November	32.9	18.6	25
December	31.2	15.5	27

Table No.(55)Mean temperature and humidity (2005-2006-2007-2008) Station : Khartoum

Month	Mean Temperature °C		Mean Relative Humidity%
	Max	Min	
January	34.1	16.4	32.3
February	35.8	17.6	24.3
March	39.6	21.4	16.6
April	40.8	24.73	21.6
May	42.5	27.9	29.3
June	41.8	26.7	42.3
July	39.9	25.2	61.3
August	38.3	23.4	57.6
September	39.8	24.5	52.6
October	41.0	24.2	33.3
November	36.96	22.2	29.3
December	37.16	19.2	37.3

Table No.(56) Mean temperature and humidity (2005-2006-2007-2008) Station: Atbara

Month	Mean Temperature °C		Mean Relative Humidity%
	Max	Min	
January	30.8	13.9	18.9
February	33.8	14.7	14.7
March	38	18.0	18.0
April	40.8	22.7	16.0
May	43.5	26.3	26.3
June	44.2	31.6	31.6
July	41.6	27.3	27.3
August	41.3	27.63	27.6
September	41.7	27.3	27.3
October	40.43	24.8	24.8
November	36.0	19.9	19.9
December	32.4	15.8	15.8

Table No.(57) Mean temperature and humidity (2005-2006-2007-2008) Station: Port Sudan

Month	Mean Temperature °C		Mean Relative Humidity%
	Max	Min	
January	27.6	21.0	60
February	28.2	20.9	63
March	30.7	21.4	60
April	33.4	24.4	58
May	37.6	27.2	40
June	40.3	30.5	31
July	41.4	31.4	35
August	42.03	29.5	35
September	41.16	31.5	44
October	36.5	28.1	65
November	31.3	24.8	65
December	28.5	22.2	61

Table No.(58) Mean temperature and humidity (2005-2006-2007-2008) Station: Elgadarif

Month	Mean Temperature °C		Mean Relative Humidity%
	Max	Min	
January	34.8	18.1	35
February	36.6	19.4	30
March	40.1	22.4	23
April	41.2	25.3	28
May	41.0	26.0	34
June	38.1	25.1	50
July	34.4	22.2	68
August	33.2	21.6	73
September	34.6	21.9	69
October	37.0	22.8	52
November	37.7	21.9	35
December	36.0	19.2	37